One Johnson & Johnson Plaza
Room WT-702
New Brunswick, NJ 08933
732-524-1851 (Telephone)
732-246-8234 (Fax)

To:
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: ***Docket No. FDA-2010-N-0348: Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations; Availability; Request for Comments***

Dear Sir/Madam:

Johnson & Johnson appreciates the opportunity to provide comments on the Center for Devices and Radiological Health's (CDRH) preliminary recommendations for strengthening the 510(k) program and improving the consistency of its decision-making, set forth in the two-volume set of documents entitled "Center for Devices and Radiological Health Preliminary Internal Evaluations" (the "Reports"). We support FDA's objectives to improve patient safety through the efficient application of predictable, risk-based, regulatory requirements.

Johnson & Johnson is a health care company that brings innovative ideas, products and services to advance the health and well-being of people around the world. Our more than 250 Johnson & Johnson companies work with partners in health care to touch the lives of over a billion people every day. The Medical Devices and Diagnostics Companies and the Consumer Companies of Johnson & Johnson have marketed a wide range of medical device and diagnostic products for over 120 years and we continue to develop novel medical technologies that advance the health and well-being of people around the world.

Our comments are composed of three parts. First, we provide general comments, which include our support of the efforts to improve the 510(k) program and detail how we look forward to helping FDA prioritize the implementation of the final adopted changes. Second, we provide specific comments on the Recommendations that we feel have the potential to critically influence (positively or negatively) our joint responsibilities to protect patient safety and promote public health through innovation. Third, we provide a summary of our position on the remaining Recommendations. For these remaining Recommendations, our position is the same as that held by AdvaMed and we refer you to their detailed comments also submitted to the above-referenced docket.

***General Comments*:**

We commend CDRH, and specifically the 510(k) Working Group (the "Working Group") and the Task Force on the Utilization of Science in Regulatory Decision Making (the "Task Force"), for their comprehensive evaluation of the 510(k) program. We agree with CDRH that the following elements are critical to an effective 510(k) program: (1) "a rational, well-defined, and consistently interpreted review standard," (2) "informed decision making," and (3) "appropriate systems and metrics…to assure quality, consistency, timeliness, and predictability." We also agree that improvements can be made in each of these areas to enhance the effectiveness of this critical regulatory program. Our assessment of many of the Recommendations in the Reports is dependent upon their appropriate implementation, which in many cases will require public notice and comment. We look forward to continuing to share our perspectives and comments with CDRH on those recommendations that are pursued once they are made more specific and their potential impact and value can be better determined.

Along with other industry members, we have important experience and perspectives to share with CDRH with respect to the feasibility of implementation and the potential impact of the proposed changes. In that regard, we appreciated CDRH's consideration of Johnson and Johnson's previous comments submitted on March 19, 2010 in response to the January 27, 2010 FDA Docket-2010-N-0054, Strengthening the Center for Devices and Radiological Health's 510(k) Review Process. Overall we believe the 510(k) process represents a long-standing, generally well functioning program that fosters innovation while protecting patient safety. This is evidenced by the tens of thousands of devices cleared since the 510(k) process was instituted and the excellent safety record to date.

In order to accomplish CDRH's three stated objectives (innovation, predictability, and improving patient safety), CDRH should focus on the most critical, high-impact recommendations that truly offer improvement in those three areas. As noted in the Reports, while the current process is working effectively to provide safe products, as with any program, the 510(k) program can benefit from improvements. However, we are concerned that simultaneously implementing more than 70 recommendations would be overwhelming, require significant resources, and detract from the high impact priorities. We urge CDRH to take a phased-in approach for developing, evaluating, and implementing the Recommendations. Any significant new processes that are established first should be piloted on a small number of products to assure that wider implementation is practical and meaningful. Metrics should be gathered to assure that the new processes actually add value (improve patient safety, foster innovation, and increase predictability) before wider implementation.

Further, in regards to implementation timelines, it is imperative that FDA consider the impact the potential modification, elimination, or addition of requirements for premarket clearance has on products currently in development. A regulatory strategy and subsequent validation testing are reliant on the chosen pathway to market. If the selected pathway suddenly ceases to be a viable option, it could result in significant delays in the availability of new or improved devices to the public.

New requirements that add substantial effort (within industry and the FDA) to the 510(k) system could impede innovation and must be limited only to the higher risk products that merit stronger requirements. For example, products that already have a long, positive safety history (including some implantables) should not fall into the proposed Class IIb (see our specific response below to CDRH's recommendation to create a Class IIb). Also, new products placed into this subset of higher risk device types should be down-classified when enough positive postmarket safety data are available.

Three critical themes are evident in the Reports: (1) review staff may not be effectively trained, (2) guidances are not sufficiently clear, and (3) CDRH underutilizes tools currently within its authority.

By initially focusing on the recommendations that correct these root issues, CDRH may eliminate the need for implementation of additional recommendations that would require new legislation or could make the program more burdensome with little or no additional benefit to the public health. Johnson & Johnson supports many of the proposals within the two Reports that were designed to address training and education of reviewers and industry to enhance program performance and predictability of the 510(k) review process. Johnson & Johnson would like to work cooperatively with CDRH to establish opportunities to provide informational access to new technologies and best practices in industry.

Specific Comments:

1. CDRH Recommendation: Definition of Substantial Equivalence

CDRH should clarify the meaning of "substantial equivalence" through guidance and training for reviewers, managers, and industry.

Johnson & Johnson Comment

Johnson & Johnson supports providing greater clarity of the meaning of "substantial equivalence" through guidance and training to both CDRH reviewers and industry. This would allow more predictable development paths, and more predictable FDA decision making, particularly with higher risk and more complex devices. Johnson & Johnson believes that the concept of substantial equivalence in the context of the 510(k) program is based on well-founded public health and scientific principles geared toward producing reasonable regulatory decisions.

While we believe that the 510(k) program is sound, we understand the need to adjust the program to address legitimate challenges and to improve consistency and predictability. It is from this perspective that we agree with many of the observations of the 510(k) working group; namely that there are elements of section 513(i) of the Act that could benefit from clarification.

Section 513(i) establishes that a medical device is substantially equivalent to a predicate device if it has *the same intended use* as the predicate device; and (1) it has the same technological characteristics as the predicate device; or (2) it has different technological characteristics which *do not raise new questions of safety and effectiveness* and is shown to be *as safe and effective* as the predicate device. Recently, as pointed out by the 510(k) working group, criticism of selected decisions has created confusion over what constitutes "the same intended use" and what questions of safety and effectiveness should be viewed as "new." Johnson & Johnson agrees that clarification of what constitutes "the same intended use" and what constitutes a "new" question of safety and effectiveness would be beneficial to both industry and FDA and would increase predictability of the 510(k) review process. Johnson & Johnson believes this clarification can be obtained through the use of amended regulations and consistent guidance language.

2. CDRH Recommendation: Same Intended Use – Lack of Clear Distinction Between Terms

The 510(k) Working Group recommends that CDRH revise existing guidance to consolidate the concepts of "indication for use" and "intended use" into a single term, "intended use," in order to reduce inconsistencies in their interpretation and application. Several public comments expressed concern that, if these two terms were combined, any proposed change in a device's label indications could be considered a change in "intended use." The Working Group recognizes the importance of providing submitters with the flexibility to propose certain changes to their labeling, without such a change necessarily constituting a new "intended use." Therefore it recommends that CDRH carefully consider what characteristics should be included under the term "intended use," so that modifications

that are currently considered to be only changes in "indications for use" and that CDRH determines do not constitute a new "intended use," are not in the future necessarily construed as changes in "intended use" merely because of a change in semantics. Any change in terminology would be intended to provide greater clarity and simplicity, not necessarily to make the concept of "intended use" more restrictive. The Center should also carefully consider what it should call the existing "Indications for Use" statement in device labeling and the "Indications for Use" form currently required for all 510(k)s, in order to avoid confusion in terminology but still maintain an appropriate level of flexibility for submitters.

Johnson & Johnson Comment

Johnson & Johnson does not agree with the recommendation to consolidate the terms: "Intended Use" and "Indications for Use." The terms "Intended Use"[1] and "Indications for Use"[2] are defined in 21 CFR 801.4 and 21 CFR 814.20(b)(3)(i), respectively, and these concepts have specific meaning within the 510(k) system. The two terms serve different purposes and should therefore remain distinct and separate.

In the context of the 510(k) framework, the practical definition of the term "intended use" refers to the general use of the device, as reflected in the representations made by the device manufacturer or seller to others in the marketing of the device. For example, the intended use of a suture is to approximate soft tissue, the intended use of an electrosurgical cutting and coagulation device is to remove tissue and control bleeding; the intended use of an intervertebral body fusion device is to fuse vertebral bodies. The practical definition of "indications for use" refers to the description of the disease/condition and patient population where the device can be used. For example, the indications for use statements for many absorbable sutures read: "(absorbable sutures) are indicated for general soft-tissue approximation but not for use in cardiovascular or neurological tissues, microsurgery or ophthalmic surgery." Furthermore, some devices may have no specific indications for use but a broad application covered solely under intended use, for example, an *in vitro* diagnostic assay that measures a specific analyte in blood (e.g., cholesterol).

It is important to keep these two terms separate and distinct. Under the current 510(k) paradigm, differences in indications for use between a predicate device and a new device are permitted if the intended uses of the two devices are the same. This paradigm provides both the flexibility to permit marketing clearance in these situations and the control to find devices "not substantially equivalent" when the differences in the indications statement alter the intended therapeutic effect. In summary, we support continued separation of terms, development of guidance to clearly identify characteristics to be included in "indications for use" and "intended use" and training for CDRH reviewers and staff on determination of intended use.

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[1] Intended Use:
"The words intended uses or words of similar import in Sec. 801.5, 801.119, and 801.122 refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer…."

[2] Indications for Use:
"A general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended."

3. CDRH Recommendation: Use of "Split Predicates" and "Multiple Predicates"

The 510(k) Working Group recommends that CDRH develop guidance on the appropriate use of more than one predicate, explaining when "multiple predicates" may be used. The Center should also explore the possibility of explicitly disallowing the use of "split predicates." In addition, CDRH should update its existing bundling guidance to clarify the distinction between multi-parameter or multiplex devices (described in Section 5.1.2.3 of this report) and bundled submissions (described in Section 4.3.4.2).

The 510(k) Working Group recommends that CDRH provide training for reviewers and managers on reviewing 510(k)s that use „multiple predicates," to better assure high-quality review of these often complex devices. The training should clarify the distinction between multi-parameter or multiplex devices and bundled submissions. In addition, CDRH should more carefully assess the impact of submissions for multi-parameter or multiplex devices and bundled submission on review times, and should consider taking steps to account for the additional complexity of these submissions as it establishes future premarket performance goals.

Johnson & Johnson Comment

Johnson & Johnson encourages CDRH to develop appropriate guidance on the use and definition of split predicates and multiple predicates. It has become apparent that much confusion exists in FDA and industry on the definition and relationships between multiple predicates, split predicates, and multi-parameter/multiplex tests.

Johnson & Johnson does not support the recommendation to explore the possibility of explicitly disallowing the use of "split predicates." Johnson & Johnson considers the ability to utilize split predicates an essential tool to aid FDA in promoting patient safety through fostering innovation and believes that use of split predicates should continue to be permitted under the 510(k) process. The use of split predicates in 510(k) submissions allows lower risk, novel device types the benefit of efficient review leading to greater patient access to innovative devices. Employing a split predicate, i.e., combining the attributes of one or more predicates in a unique way to provide evidence of substantial equivalence for a new device, can result in a device that has the potential to streamline medical care or otherwise advance the public health. Utilization of split predicates in the 510(k) program is an alternative to the *de novo* process, and allows low-risk, novel devices to be evaluated for marketing clearance in an efficient and effective manner. To obviate FDA's concern that use of split predicates reduces or impairs their ability to review the safety and effectiveness of the new device, Johnson & Johnson proposes that FDA consider the use of risk assessments (ISO 14971:2009) to demonstrate that risks associated with the new device have been evaluated and mitigated to an acceptable level.

Johnson & Johnson supports the recommendation for CDRH to provide training for reviewers and managers on the use of multiple predicates to assist in their reviews. We believe this training will assist reviewers and managers to meet the statutory review times and potentially decrease the number of review cycles. Again, clear definitions of multiple predicates and spilt predicates should be provided in guidance for FDA and industry. In addition, this guidance should include the required content for a multiple or split predicate submission. For example, split predicate should have a requirement for a risk assessment; multiple predicates must have the same intended use, etc. With well written guidance and training, this type of submission could still be reviewed within FDA's current review goals.

Johnson & Johnson requests that FDA keep the current Bundling Guidance intact (Guidance for Industry and FDA Staff: Bundling Multiple Devices or Multiple Indications in a Single Submission, June 22, 2007), and not confound it with additional proposed guidance concerning use of multi-parameter or multiplex devices. A bundled submission allows for an efficient review for more than one

new device under one submission, when the new devices have similar supporting data and indications for use. This is an asset for both FDA and industry in terms of efficiency and application to current technology. Johnson & Johnson believes that the current guidance is clear and we support reviewer training on the existing guidance to ensure consistent application.

Johnson & Johnson agrees with the Working Group's recommendation that CDRH needs to conduct additional analyses to prove or disprove the Working Group's hypothesis of an association between citing more than 5 predicates and a greater mean rate of AE reports. These analyses should distinguish use of "multiple predicates" and "split predicates." These analyses should be performed before development or issuance of CDRH guidance on the use of predicates to determine whether the use of multiple or split predicates is an overarching root cause to higher AE rates. The percentage of device recalls should be assessed in a similar manner, and these analyses should be transparent to industry.

4. CDRH Recommendation: *de novo* Classification

CDRH should reform its implementation of the* de novo *classification process to provide a practical, risk-based option that affords an appropriate level of review and regulatory control for eligible devices.

The 510(k) Working Group recommends that CDRH revise existing guidance to streamline the current implementation of the* de novo *classification process and clarify its evidentiary expectations for* de novo *requests. The Center should encourage pre-submission engagement between submitters and review staff to discuss the appropriate information to provide to CDRH for devices eligible for* de novo *classification, potentially in lieu of an exhaustive 510(k) review. The Center should also consider exploring the possibility of establishing a generic set of controls that could serve as baseline special controls for devices classified into Class II through the* de novo *process, and which could be augmented with additional device-specific special controls as needed.

Johnson & Johnson Comment

Johnson & Johnson agrees with the 510(k) Working Group recommendation that FDA should streamline the *de novo* classification process and clarify content expectations/requirements. Making the *de novo* process transparent and predictable would be beneficial to both FDA and industry and may allow more products to be filed using the *de novo* process. This should lead to shorter review times, reduced resource requirements more appropriate for a Class I or Class II risk compared to a PMA review, thus allowing greater patient access to innovative products. We suggest FDA implement use of a pre-review process for a *de novo* submission (i.e., a "pre-IDE"), where FDA and the sponsor agree to use of the *de novo* process as a viable pathway as well as to content requirements of the *de novo* submission. Early utilization of a scientific panel of experts, when needed, could benefit this pre-review. We suggest that the sponsor requesting the *de novo* classification be required to provide completed hazard analysis in the "pre-IDE" document and a decision making matrix or algorithm, using FDA-recommended templates, which would be based on ISO 14971:2009.

Johnson & Johnson agrees that the content of the *de novo* submission needs to include supportive evidence to allow the Agency to fully evaluate the risks and benefits of the device. Clinical trials or clinical data should not be an outright requirement of a *de novo* submission; however, the hazard analysis and decision-making matrix should clearly document why these studies are or are not required.

As identified in the report, a generic special control for devices reviewed under *de novo* is a good step to strengthening the process. A generic set of special controls similar to the Global Harmonization Task Force (GHTF) Essential Principles would provide a means to create a consistent evidentiary standard for *de novo* reviews, and would minimize movements toward full PMA set requirements - as the *de novo*

process was intended to be an abbreviated process for lower risk, new intended uses. Further, to increase consistency in the process we recommend the creation of a template identifying these generic special controls.

Again, as noted in the Report, we agree there is merit in minimizing the time spent on the 510(k) review for a product that clearly is *de novo*. The review should focus on what additional information may be needed for the next level review. FDA should clearly communicate to the manufacturer the requirements to meet *de novo* classification and communication could include the use of submission meetings, where appropriate. Here, again, the use of a generic set of special controls similar to the GHTF principles will assist in streamlining this process.

Lastly, because of the importance of developing this pillar of FDA's regulatory framework, we recommend the agency consider holding public meetings on the streamlined *de novo* process.

Please refer to previous comments submitted by Johnson and Johnson to FDA Docket -2010-N-0054 Strengthening the Center for Devices and Radiological Health's 510(k) Review Process, providing recommendations on updating the current *de novo* guidance to include a prescribed hazard analysis format along with a decision-making matrix or algorithm.

5. CDRH Recommendation: Type and Level of Evidence Needed

The 510(k) Working Group recommends that CDRH develop guidance defining a subset of Class II devices, called "Class IIb" devices, for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting, would typically be necessary to support a substantial equivalence determination.

Johnson & Johnson Comment

Johnson & Johnson does not support the proposed Class IIb subset as defined in the Reports and in subsequent comments by CDRH Leadership in the August 31, 2010 webinar on Draft 510(k) and Use of Science in Regulatory Decision Making Reports. Contrary to providing transparency and predictability to the regulatory process, the addition of the proposed Class IIb subset may be cause for confusion between the current PMA regulatory process and the proposed higher risk Class IIb process. The elements FDA has identified as being part of Class IIb requirements, i.e., a pre-approval inspection, periodic reporting, submission of manufacturing information, submission of Safety and Effectiveness data, and post-approval commitments, are presently PMA requirements.

The 510(k) Working Group recommendation states that "delineating between Class IIa and Class IIb would not reconfigure the current, three-tiered device classification system established by statute, it would only be an administrative distinction." However, other recommendations in the report and recent public comments by CDRH leadership further describing Class IIb are more in line with a new tier rather than an "administrative distinction" within the Class II tier. Rather than creating a new Class IIb, a clear risk-based approach within Class II would better serve to protect public health and safety while promoting product innovations. Adopting this approach also serves to move the FDA regulation of devices in the same direction as initiatives being implemented by the GHTF. Further, it would link to proposals for the revision of the IVD Directive in Europe which also is proposing a risk-based classification system. This alignment will facilitate a common understanding of regulatory requirements for industry as a whole.

Johnson & Johnson could support a narrower interpretation related to a subset of Class II devices as described in the original AdvaMed proposal for identification of Class II device types that warrant special controls. We recognize the potential value of creating guidance for a specified subset of higher-risk

device types for which additional information would typically be necessary to support a substantial equivalence determination.

As this concept is further developed, it should be addressed in the larger context of the different types of 510(k) submissions within the current program, specifically Special 510(k), Abbreviated 510(k), and Traditional 510(k). The evidentiary requirements for this subset of Class II devices should be consistent with the legal framework in place for Class II devices. Any special requirements should be applied on a product-specific basis and only when needed to determine substantial equivalence. A process already exists to allow inclusion of a special control in the device classification regulation which then makes the special control applicable to that individual device type.

Clinical evidence requirements should only apply to those devices that require clinical data to establish a safety profile to support a determination of substantial equivalence. Clinical evidence requirements should only be applied when other means of establishing safety (i.e., preclinical bench, laboratory and animal studies, ex-US clinical data, literature, etc.) are exhausted or prove to be insufficient. We encourage CDRH to consider the recognition of international consensus standards, specifically ISO 14155, which describes the methodology to collect clinical evidence through literature review and other means, such as simulated clinical use studies. Manufacturing information requirements should be limited to a high level description of the manufacturing process and a flow diagram outlining the key manufacturing steps, which is sufficient to support a substantial equivalence determination for a device.

Johnson & Johnson does not agree with OIVD's public comment, during the August 31, 2010 Webinar, that all Class II *in vitro* diagnostic devices that require clinical data should be classified in the higher risk subset of Class IIb. AdvaMed has provided FDA with a draft guidance on how to increase transparency and predictability within the current regulations for *in vitro* diagnostic tests (**DRAFT Guidance – Risk-Based Assessment of *In Vitro* Diagnostic Tests, submitted to FDA April 22, 2010).** This document is initially intended to provide guidance to the Office of *In Vitro* Diagnostic Device Evaluation and Safety (OIVD) personnel and to manufacturers to further outline the appropriate regulatory strategy for the content and review process for IVD submissions. This approach can be applied to all medical devices and is founded on fundamental and well-established, risk-based approaches to regulation set out by the Office of Device Evaluation in 1993 and by the Division of Clinical Laboratory Devices (DCLD, the precursor to OIVD) in 1996. This method is also utilized as contemporary principles of risk management, such as those contained in ISO Standard 14971: 2009 and core principles for modernization of the diagnostics regulatory process. These principles have been discussed in various policy forums, such as the Secretary's Advisory Committee on Genetics, Health and Society, and the President's Council of Advisors on Science and Technology.

We recognize that this concept of a limited Class II higher risk device subset could be an important element to improving the public confidence in the 510(k) program and we look forward to working with CDRH to further develop this concept.

6. CDRH Recommendation: Incomplete Information – Submission of All Scientific Information

The 510(k) Working Group recommends that CDRH consider revising 21 CFR 807.87, to explicitly require 510(k) submitters to provide a list and brief description of all scientific information regarding the safety and/or effectiveness of a new device known to or that should be reasonably known to the submitter. The Center could then focus on the listed scientific information that would assist it in resolving particular issues relevant to the 510(k) review.

Johnson & Johnson Comment

Johnson & Johnson does not support this recommendation. Routine submission of scientific data for all 510(k) submissions would be burdensome on both industry and CDRH, without benefit to public health and safety and, in fact, would distract FDA reviewers from careful review of the critical subset of information related to higher risk devices. Therefore, the scope of this recommendation for scientific data should be limited to a specified high risk subset of Class II devices, where the information may be relevant to a determination of substantial equivalence.

It would be helpful to consider the types of information that would be most useful to reviewers in making a substantial equivalence determination. It seems clear from the example provided that CDRH is seeking information not publicly available and found within the submitter's internal documents, such as additional clinical studies and information from the Design History File directly relevant to the device being reviewed. It may be reasonable to ask a submitter to include a brief summary of information from market experience with the same device in markets outside the US, if any. CDRH itself has access to information in published, peer-reviewed literature, as well as information on MDRs and recalls which, in the case of a new device not yet on the market in the US, would not be relevant. It is not clear from the recommendation whether a summary of this type of publicly available information would be expected as part of a listing and brief description of all scientific information.

FDA should explicitly exclude from this requirement information about the iterative design process of the device in the application. Early prototypes are frequently modified, enhanced, strengthened and improved during the design and testing processes, and these early iterations and their performance are not relevant for review of the 510(k) of the final device. FDA also would have access to this information because these iterations and test results can be found in the Design History File, which are subject to review during routine QSR audits.

A final consideration for CDRH is whether a requirement for all scientific information could be implemented without statutory change. FDA may request scientific information regarding safety and effectiveness about a device when that information can be shown to be germane to the substantial equivalence determination. If the information is not necessary to make a substantial equivalence determination, FDA may not request it without a statutory change.

7. CDRH Recommendation: Periodic Reporting Requirements – Labeling

CDRH should revise existing regulations to clarify the statutory listing requirements for the submission of labeling. CDRH should also explore the feasibility of requiring manufacturers to electronically submit final device labeling to FDA by the time of clearance or within a reasonable period of time after clearance, and also to provide regular, periodic updates to device labeling, potentially as part of annual registration and listing or through another structured electronic collection mechanism.

Johnson & Johnson Comment

Johnson & Johnson does not support this recommendation as stated. The creation of a 510(k) labeling database is duplicative of efforts already underway within the Unique Device Identifier (UDI) System. The scope and complexity of this effort is grossly underestimated by the 510(k) Working Group. For the great majority of 510(k) cleared devices, there is no value added for FDA to review the final printed labeling, and to require this would add time to the final approval without any demonstrated benefit to patient safety.

We strongly believe that dissemination of labeling to patients or clinicians should be the responsibility of the manufacturer. Most labeling changes are insignificant to CDRH review (such as additional languages, minor typographical corrections and formatting) and submission and review of them would have no benefit to public safety. General public access to that labeling would lead to further public confusion if the labeling dissemination was not controlled by the manufacturer.

Additional Specific Comments:

In addition to the general and specific comments provided above, Johnson & Johnson is providing a summary of our position for the remaining Recommendations within the Reports. The listings below are divided into three categories: (1) Recommendations on which we are in alignment with the CDRH, (2) those which we can support with suggested modification, and (3) those which Johnson & Johnson does not support and feels may not be in the interest of promotion of patient health and safety. Johnson & Johnson refers CDRH to the AdvaMed comments posted to this same docket for details on our position on the Recommendations listed below as their position is similar to ours.

For those recommendations that Johnson & Johnson supports, we agree they are of importance in advancing the key objectives of improvements to the 510(k) program and will aid in improving patient safety while promoting device innovations and enhanced regulatory predictability.

For recommendations that Johnson & Johnson supports with suggested modification, FDA will need to provide further information on the specific recommendations and careful consideration will need to be given regarding the scope and timing of implementation to assure that the changes will foster innovation and promote public health and safety. Implementation of many of these recommendations will require further public notice and comment and Johnson & Johnson looks forward to continuing to share our perspectives with CDRH on these promising recommendations.

For those recommendations that Johnson & Johnson does not support as currently written, we have concerns that the proposed changes will significantly impact current effective and appropriately rigorous regulatory pathways, will not improve assurance of safety and effectiveness of the device, and may potentially impede Medical Device development and the mutual goal of bringing the best health care technologies to the patients.

Summary of Johnson & Johnson Positions on the Working Group Recommendations

Recommendations Johnson & Johnson Supports

The 510(k) Working Group recommends that CDRH:
Revise existing guidance to provide clear criteria for identifying ―different questions of safety and effectiveness" and to identify a core list of technological changes that generally raise such questions (e.g., a change in energy source, a different fundamental scientific technology). **(J&J specific comments above)**
Clarify the meaning of ―substantial equivalence" through guidance and training for reviewers, managers, and industry. **(J&J specific comments above)**
Develop and provide training for reviewers and managers on how to determine whether a 510(k) raises ―different questions of safety and effectiveness." Training on ―different technological characteristics" and ―different questions of safety and effectiveness" should also be provided to industry.
Revise existing guidance to streamline the current implementation of the *de novo* classification process and clarify its evidentiary expectations for *de novo* requests. The Center should encourage pre-submission engagement between submitters and review staff to discuss the appropriate information to provide to CDRH for devices eligible for *de novo* classification, potentially in lieu of an exhaustive 510(k) review. The Center should also consider exploring the possibility of establishing a generic set of controls that could serve as baseline special controls for devices classified into class II through the *de novo* process, and which could be augmented with additional device-specific special controls as needed. **(J&J specific comments above)**
Revise existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k), and, for those modifications that do warrant a new 510(k), what modifications are eligible for a Special 510(k).
Provide additional guidance and training for submitters and review staff regarding the appropriate use of consensus standards, including proper documentation with a 510(k).
Develop guidance and Standard Operating Procedures (SOPs) on the development and assignment of product codes, in order to standardize these processes and to better address the information management needs of the Center's staff and external constituencies.
Further enhance existing staff training on the development and assignment of product codes.
Develop guidance and SOPs for the development of 510(k) summaries to assure they are accurate and include all required information identified in 21 CFR 807.92. The Center should consider developing a standardized electronic template for 510(k) summaries.
Develop guidance and regulations regarding appropriate documentation of transfers of 510(k) ownership. The Center should update its 510(k) database in a timely manner when a transfer of ownership occurs.
Continue to take steps to enhance recruitment, retention, training, and professional development of review staff, including providing opportunities for staff to stay abreast of recent scientific developments and new technologies. This should include increased engagement with outside experts.

The 510(k) Working Group recommends that CDRH:
Consider establishing a Center Science Council comprised of experienced reviewers and managers and under the direction of the Deputy Center Director for Science. The Science Council should serve as a cross-cutting oversight body that can facilitate knowledge-sharing across review branches, divisions, and offices, consistent with CDRH's other ongoing efforts to improve internal communication and integration.
Further enhance its third-party reviewer training program and consider options for sharing more information about previous decisions with third-party reviewers, in order to assure greater consistency between in-house and third-party reviews.
Develop metrics to continuously assess the quality, consistency, and effectiveness of the 510(k) program, and also to measure the effect of any actions taken to improve the program. As part of this effort, the Center should consider how to make optimal use of existing internal data sources to help evaluate 510(k) program performance.
The 510(k) Working Group further recommends that CDRH conduct additional analyses to determine the basis for the apparent association between citing more than five predicates and a greater mean rate of adverse event reports, as shown in Section 5.1.2.3 of this report.

Recommendations Johnson & Johnson Supports with Modifications

The 510(k) Working Group recommends that CDRH:	**J&J Requested Modifications**
Carefully consider what it should call the existing ―Indications for Use" statement in device labeling and the ―Indications for Use" form currently required for all 510(k)s, in order to avoid confusion in terminology but still maintain an appropriate level of flexibility for submitters.	Include indications for use in labeling but not label
Develop or revise existing guidance to clearly identify the characteristics that should be included in the concept of ―intended use."	Revise existing guidance to clarify terms, not consolidate terms
Provide training for reviewers and managers on how to determine ―intended use." Such training should clarify the elements of a device application that should be considered when determining the ―intended use," e.g., product labeling, device design (explicit or implied), literature, and existing preclinical or clinical data. Training on ―intended use" should also be provided to industry.	Reviewers should be trained on how to determine both terms
Develop guidance on the appropriate use of more than one predicate, explaining when ―multiple predicates" may be used.	**J&J specific comments above**

The 510(k) Working Group recommends that CDRH:	J&J Requested Modifications
Provide training for reviewers and managers on reviewing 510(k)s that use ―multiple predicates," to better assure high-quality review of these often complex devices. The training should clarify the distinction between multi-parameter or multiplex devices and bundled submissions. In addition, CDRH should more carefully assess the impact of submissions for multi-parameter or multiplex devices and bundled submission on review times, and should consider taking steps to account for the additional complexity of these submissions as it establishes future premarket performance goals.	**J&J specific comments above**
Explore the possibility of requiring each 510(k) submitter to provide as part of its 510(k) detailed photographs and schematics of the device under review, in order to allow review staff to develop a better understanding of the device's key features. Currently, CDRH receives photographs or schematics as part of most 510(k)s; however, receiving both as a general matter would provide review staff with more thorough information without significant additional burden to submitters.	Request only when needed for determination of substantial equivalence
Explore the possibility of requiring each 510(k) submitter to keep at least one unit of the device under review available for CDRH to access upon request, so that review staff could, as needed, examine the device hands-on as part of the review of the device itself, or during future reviews in which the device in question is cited as a predicate.	Request only when needed for determination of substantial equivalence
As part of the ―Class IIb" guidance, provide greater clarity regarding the circumstances in which it will request clinical data in support of a 510(k), and what type and level of clinical data are adequate to support clearance. CDRH should, within this guidance or through regulation, define the term ―clinical data" to foster a common understanding among review staff and submitters about types of information that may constitute ―clinical data." General recommendations related to the least burdensome provisions, premarket data quality, clinical study design, and CDRH's mechanisms for pre-submission interactions, including the pre-IDE and IDE processes, are discussed further in the preliminary report of the Center's Task Force on the Utilization of Science in Regulatory Decision Making (described further in Section 2, below). That report also recommends steps CDRH should take to make well-informed, consistent decisions, including steps to make better use of external experts.	Support greater clarity of circumstances and definition of clinical data. All IVD's should not be placed in ―Class IIb." (**Also see J&J specific comments above)**
Explore greater use of its postmarket authorities, and potentially seek greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices.	Support exploring current authority
Continue its ongoing effort to implement a unique device identification (UDI) system and consider, as part of this effort, the possibility of using ―real-world" data (e.g., anonymized data on device use and outcomes pooled from electronic health record systems) as part of a premarket submission for future 510(k)s.	Premature to consider submission of data from electronic records

The 510(k) Working Group recommends that CDRH:	J&J Requested Modifications
Develop guidance to provide greater clarity regarding what situations may warrant the submission of manufacturing process information as part of a 510(k), and include a discussion of such information as part of its ~~"c~~lass IIb" guidance.	Should apply to only a small subset; should be summary information; should not include IVD products (**Also see J&J specific comments above)**
Clarify when it is appropriate to use its authority to withhold clearance on the basis of a failure to comply with good manufacturing requirements in situations where there is a substantial likelihood that such failure will potentially present a serious risk to human health . . .	Clarify when it is appropriate to use its current authority to withhold clearance
Develop a publicly available, easily searchable database that includes, for each cleared device, a verified 510(k) summary, photographs and schematics of the device, to the extent that they do not contain proprietary information, and information showing how cleared 510(k)s relate to each other and identifying the premarket submission that provided the original data or validation for a particular product type.	Photographs and schematics should not be included in the public database
Periodically audit 510(k) review decisions to assess adequacy, accuracy, and consistency. The ongoing implementation of iReview (described in Section 5.3.2 of this report), as part of the Center's FY 2010 Strategic Priorities, could assist with this effort by allowing CDRH to more efficiently search and analyze completed reviews. These audits should be overseen by the new Center Science Council, described above, which would also oversee the communication of lessons learned to review staff, as well as potential follow-up action.	Define objective of audit and authority of Council; do not support authority to reverse decisions

Recommendations Johnson &Johnson Does not Support

The 510(k) Working Group recommends that CDRH:
Revise existing guidance to consolidate the concepts of ~~"i~~ndication for use" and ~~"in~~tended use" into a single term, ~~"i~~ntended use," in order to reduce inconsistencies in their interpretation and application. Several public comments expressed concern that, if these two terms were combined, any proposed change in a device's label indications could be considered a change in ~~"in~~tended use." **(J&J specific comments above)**
In addition to the guidance on the appropriate use of more than one predicate, should update its existing bundling guidance to clarify the distinction between multi-parameter or multiplex devices (described in Section 5.1.2.3 of this report) and bundled submissions (described in Section 4.3.4.2). **(J&J specific comments above)**
Explore the possibility of pursuing a statutory amendment to section 513(i)(1)(E) of the Federal, Food, Drug and Cosmetic Act ... that would provide the agency with the express authority to consider an off-label use, in certain limited circumstances, when determining the ~~"in~~tended use" of a device under review through the 510(k) process.

The 510(k) Working Group recommends that CDRH:
Reconcile the language in its 510(k) flowchart (shown on page 27 of this report) with the language provided in section 513(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360c(i) regarding "different technological characteristics" and "different questions of safety and efficacy."
Consider developing guidance on when a device should no longer be available for use as a predicate because of safety and/or effectiveness concerns. It is expected that such a finding would be an uncommon occurrence. Any factors set forth in guidance regarding when a device should no longer be used as a predicate should be well-reasoned, well-supported, and established with input from a range of stakeholders, and unintended consequences should be carefully considered.
Consider issuing a regulation to define the scope, grounds, and appropriate procedures, including notice and an opportunity for a hearing, for the exercise of its authority to fully or partially rescind a 510(k) clearance. As part of this process, the Center should also consider whether additional authority is needed.
Explore the possibility of explicitly disallowing the use of "split predicates." **(J&J specific comments above)**
Explore the feasibility of requiring each manufacturer to provide regular, periodic updates to the Center listing any modifications made to its device without the submission of a new 510(k), and clearly explaining why each modification noted did not warrant a new 510(k). The Center could consider phasing in this requirement, applying it initially to the "class IIb" device subset described in Section 5.2.1.3, below, for example, and expanding it to a larger set of devices over time.
Consider adopting the use of an "assurance case" framework for 510(k) submissions. An "assurance case" is a formal method for demonstrating the validity of a claim by providing a convincing argument together with supporting evidence. It is a way to structure arguments to help ensure that top-level claims are credible and supported. If CDRH pursues this approach, the Center should develop guidance on how submitters should develop and use an assurance case to make adequate, structured, and well-supported predicate comparisons in their 510(k)s. The guidance should include the expectation that all device description and intended use information should be submitted and described in detail in a single section of a 510(k). The guidance should also clearly reiterate the long-standing expectation that 510(k)s should describe any modifications made to a device since its previous clearance. CDRH should also develop training for reviewers and managers on how to evaluate assurance cases.
Include photographs and schematics, to the extent that they do not contain proprietary information, as part of its enhanced public 510(k) database, described below, to allow prospective 510(k) submitters to develop a more accurate understanding of potential predicates. Exceptions could be made for cases in which a photograph or schematic of the device under review will not provide additional useful information, as in the case of software-only devices.
Consider revising the requirements for "declaration of conformity" with a standard, for example by requiring submitters to provide a summary of testing to demonstrate conformity, if they choose to make use of a "declaration of conformity."
Consider revising 21 CFR 807.87 to explicitly require 510(k) submitters to provide a list and brief description of all scientific information regarding the safety and/or effectiveness of a new device known to or that should be reasonably known to the submitter. The Center could then focus on the listed scientific information that would assist it in resolving particular issues relevant to the 510(k) review. **(J&J specific comments above)**

The 510(k) Working Group recommends that CDRH:
Develop guidance defining a subset of class II devices, called "class IIb" devices, for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting; would typically be necessary to support a substantial equivalence determination. **(J&J specific comments above)**
Explore greater use of its postmarket authorities, and potentially seek greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices. If CDRH were to obtain broader authority to require condition-of-clearance studies, the Center should develop guidance identifying the circumstances under which such studies might be appropriate, and should include a discussion of such studies as part of its "class IIb" guidance. **(Do not support expanding authority to require condition of clearance studies)**
Clarify when it is appropriate to use its authority to . . . include a discussion of pre-clearance inspections as part of its "class IIb" guidance. **(J&J specific comments above)**
Revise existing regulations to clarify the statutory listing requirements for submission of labeling. CDRH should also explore the feasibility of requiring manufacturers to electronically submit final device labeling to FDA by the time of clearance or within a reasonable period of time after clearance, and also to provide regular, periodic updates to device labeling, potentially as part of annual registration and listing or through another structured electronic collection mechanism. **(J&J specific comments above)**
Develop a process for regularly evaluating the list of device types eligible for third-party review and adding or removing device types as appropriate based on available information. The Center should consider, for example, limiting eligibility to those device types for which device-specific guidance exists, or making ineligible selected device types with a history of design-related problems.

Summary of Johnson & Johnson positions on the Task Force Recommendations

Recommendations Johnson & Johnson Supports

The Task Force recommends that CDRH:
Work to better characterize the root causes of existing challenges and trends in IDE decision making, including evaluating the quality of its pre-submission interactions with industry and taking steps to enhance these interactions as necessary. For example, the Center should assess whether there are particular types of IDEs that tend to be associated with specific challenges, and identify ways to mitigate those challenges. As part of this process, CDRH should consider developing guidance on pre-submission interactions between industry and Center staff to supplement available guidance on pre-IDE meetings.

The Task Force recommends that CDRH:
Continue ongoing efforts to develop better data sources, methods, and tools for collecting and analyzing meaningful postmarket information, consistent with the Center's FY 2010 Strategic Priorities. In addition, the Center should conduct a data gap analysis and a survey of existing U.S. and international data sources that may address these gaps. These efforts should be in sync with and leverage larger national efforts. As CDRH continues its efforts to develop better data sources, methods, and tools, it should invite industry and other external constituencies to collaborate in their development and to voluntarily provide data about marketed devices that would supplement the Center's current knowledge.
Conduct an assessment of its staffing needs to accomplish its mission-critical functions. The Center should also work to determine what staff it will need to accommodate the anticipated scientific challenges of the future. CDRH should also take steps to enhance employee training and professional development to assure that current staff can perform their work at an optimal level. As part of this process, the Center should consider making greater use of professional development opportunities such as site visits or other means of engagement with outside experts in a variety of areas, including clinical care, as described below. This recommendation complements the Center's ongoing efforts under its FY 2010 Strategic Priorities to enhance the recruitment, retention, and development of high-quality employees.
Continue the integration and knowledge management efforts that are currently underway as part of the Center's FY 2010 Strategic Priorities. As part of these efforts, the Task Force recommends that CDRH develop more effective mechanisms for cataloguing the Center's internal expertise, assess the effectiveness of the inter-Office/Center consult process, and enhance the infrastructure and tools used to provide meaningful, up-to-date information about a given device or group of devices to Center staff in a readily comprehensible format, to efficiently and effectively support their day-to-day work.
Assess best-practices for staff engagement with external experts and develop standard business processes for the appropriate use of external experts to assure consistency and address issues of potential bias. As part of this process, the Center should explore mechanisms, such as site visits, through which staff can meaningfully engage with and learn from experts in a variety of relevant areas, including clinical care. In addition to supporting interaction at the employee level, the Center should also work to establish enduring collaborative relationships with other science-led organizations.
Enhance its data sources, methods, and capabilities to support evidence synthesis and quantitative decision making as a long-term goal.

Recommendations Johnson & Johnson Supports with Modifications

The Task Force recommends that CDRH:	J&J Requested Modifications
Assess and better characterize the major sources of challenge for Center staff in reviewing IDEs within the mandatory 30-day timeframe, and work to develop ways to mitigate identified challenges under the Center's existing authorities.	Do not expend valuable resources; develop guidance for pre-IDE meetings

The Task Force recommends that CDRH:	J&J Requested Modifications
Consider creating a standardized mechanism whereby review Offices could rapidly assemble an ad hoc team of experienced review staff from multiple divisions to temporarily assist with time-critical work in a particular product area, as needed, in order to accommodate unexpected surges in workload. This would need to be done in such a way that ad hoc teams would only assist with work that does not require specialized subject matter expertise beyond what the team members possess. The Task Force recognizes that such an approach is only a stop-gap solution to current workload challenges, and that additional staff will be necessary to better accommodate high workloads in the long term.	Ensure routine work is not adversely affected; ensure oversight of team work
Develop a web-based network of external experts using social media technology, consistent with the Center's FY 2010 Strategic Priorities, in order to appropriately and efficiently leverage external expertise that can help Center staff better understand novel technologies, address scientific questions, and enhance the Center's scientific capabilities.	Explain use of social media technology; ensure confidentiality of information
Continue its ongoing efforts to improve the quality of the design and performance of clinical trials used to support premarket approval applications (PMAs), in part by developing guidance on the design of clinical trials that support PMAs and establishing an internal team of clinical trial experts who can provide support and advice to other CDRH staff, as well as to prospective investigational device exemption (IDE) applicants as they design their clinical trials. The Center should work to assure that this team is comprised of individuals with optimal expertise to address the various aspects of clinical trial design, such as expertise in biostatistics or particular medical specialty areas. The team would be a subset of the Center Science Council discussed in Section 4.2.1 of this report, and, as such, it may also serve in the capacity of a review board when there are differences of opinion about appropriate clinical trial design and help assure proper application of the least burdensome principle. CDRH should also continue to engage in the development of domestic and international consensus standards, which, when recognized by FDA, could help establish basic guidelines for clinical trial design, performance, and reporting. In addition, CDRH should consider expanding its ongoing efforts related to clinical trials that support PMAs, to include clinical trials that support 510(k)s.	Include all stakeholders in development of guidance
Revise its 2002 "least burdensome" guidance to clarify the Center's interpretation of the "least burdensome" provisions of the Federal Food, Drug, and Cosmetic Act (21 USC §360c(a)(3)(D)(ii) and 21 USC §360c(i)(1)(D)). CDRH should clearly and consistently communicate that, while the "least burdensome provisions" are, appropriately, meant to eliminate unjustified burdens on industry, such as limiting premarket information requests to those that are necessary to demonstrate reasonable assurance of safety and effectiveness or substantial equivalence, they are not intended to excuse industry from pertinent regulatory obligations nor to lower the Agency's expectations with respect to what is necessary to demonstrate that a device meets the relevant statutory standard.	No need to revise guidance; train industry and FDA on existing guidance.

The Task Force recommends that CDRH:	J&J Requested Modifications
Develop and implement a business process for responding to new scientific information in alignment with a conceptual framework comprised of four basic steps: (1) detection of new scientific information; (2) escalation of that information for broader discussion with others; (3) collaborative deliberation about how to respond; and (4) action commensurate to the circumstance — including, potentially, deciding to take no immediate action.	Manufacturers of the products should be included on steps 3 (deliberation) and 4 (determining action) when "action" affects distributed products
Continue its ongoing efforts to streamline its processes for developing guidance documents and regulation, consistent with the Center's FY 2010 Strategic Priorities. For example, CDRH should explore greater use of the "Level 1 – Immediately in Effect" option for guidance documents intended to address a public health concern or lessen the burden on industry. CDRH should also encourage industry and other constituencies to submit proposed guidance documents, which could help Center staff develop Agency guidance more quickly.	Level 1 guidance should be reserved for when there is an urgent and documented public health issue that must be immediately addressed; Have more extensive engagement of industry in the development of guidances
Establish as a standard practice sending open "Notice to Industry" letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations on the basis of new scientific information. CDRH should adopt a uniform template and terminology for such letters, including clear and consistent language to indicate that the Center has changed its regulatory expectations, the general nature of the change, and the rationale for the change.	CDRH to provide additional information to its external constituencies about its process for determining an appropriate response to new science and the bases for its actions
Take steps to improve medical device labeling, and to develop an online labeling repository to allow the public to easily access this information. The possibility of posting up-to-date labeling for 510(k) devices online is described in greater detail in the preliminary report of the 510(k) Working Group (described further in Section 3, below).	Concerns about the feasibility and value of on-line labeling repository. Also see comments on labeling for Working Group above
Develop and make public a Standard Operating Procedure (SOP) that describes the process the Center will take to determine the appropriate response to new scientific information, based on the conceptual framework outlined above.	All stakeholders be involved in developing the standard operating procedure
Continue its ongoing efforts to make more meaningful and up-to-date information about its regulated products available and accessible to the public through the CDRH Transparency Website, consistent with the Center's FY 2010 Strategic Priorities and the work of the FDA Transparency Task Force. In addition to the pre- and postmarket information that is already available on CDRH Transparency Website, the Center should move to release summaries of premarket review decisions it does not currently make public (e.g., ODE 510(k) review summaries) and make public the results of post-approval and Section 522 studies that the Center may legally disclose.	Reviewer summaries of only cleared devices should be released

Summary and Conclusion

In the Medical Device Amendments of 1976, Congress recognized that medical devices vary widely, with different levels of risk and complexity, and that there are large numbers of new products and product improvements every year. The 510(k) Paradigm is a versatile, flexible process that allows for evolutionary change of legally-marketed Class I and Class II medical devices. Improvements in the predictability, reliability, and efficiency of 510(k) regulatory pathways can help provide safer, more effective, innovative devices and diagnostics to patients more quickly to advance their health and well being.

We appreciate the opportunity to provide feedback on these issues related to the 510(k) program. We look forward to the additional information to be provided by FDA regarding potential administrative changes to the 510(k) program, and expect to continue providing our input as both FDA and industry identify ways to strengthen the program while both protecting patient safety and fostering innovation in medical products and health care solutions. We are particularly eager to partner with the FDA in the formulation of an efficient and effective implementation plan that allows smooth adoption of improvements to the 510(k) process. If you have questions or need further clarification, please contact the undersigned at 732-524-1941.

Sincerely,

Harlan Weisman, M.D.

Chief Science and Technology Officer
Medical Devices & Diagnostics
Johnson & Johnson

October 4, 2010

California Healthcare Institute Comments Regarding the Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations.

Docket No. FDA-2010-N-0348

I. INTRODUCTION

The California Healthcare Institute (CHI) welcomes this opportunity to comment on the Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) 510(k) Working Group Preliminary Report and Recommendation, and the Task Force Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations.

A. Description of CHI

CHI represents the broad biomedical sector of the California economy and unites more than 270 of California's leading universities and private research institutes, venture capital firms and life sciences companies in support of biomedical science and biopharmaceutical and medical technology innovation. California is home to nearly **1,300** medical technology firms alone, more than any other state in the nation. The more than **112,000** medical technology jobs in California represent roughly one-third of the total U.S. medical technology workforce as well as the largest segment (41 percent) of the total **275,000** California life sciences jobs,[1] including medical technology, biopharmaceuticals, academic research, etc. It is also, most significantly, the source of many of the medical technologies that improve patient and public health around the world such as in diagnosing and treating diabetes, cardiovascular disease, cancer, hearing and vision loss, pain management and numerous other diseases and conditions.

B. Why CHI has a Unique Perspective

CHI represents the entire continuum of medical technology innovation in California. This includes basic research undertaken in our state's universities and private research institutes, which is then spun-out to venture capital-backed start-up firms. In fact, the vast majority of the medical technology companies in California are such smaller, venture capital-backed firms with fewer than 50 employees. In 2009, these

[1] CHI, California Biomedical Industry 2010 Report, available at http://www.chi.org/uploadedFiles/Report_2010_California_Biomedical_Industry_Report_FINAL.PDF

firms received $1.192 billion in medical technology VC investment, or 47 percent of the total $2.511 billion in total medical technology venture capital nationwide[2]. These smaller entrepreneurial firms are then themselves often the source of new technologies or technology advancements for larger multinationals headquartered not only in California but across the nation.

C. Importance of 510(k) to CHI Members

The 510(k) Premarket Notification process is the clearance mechanism by which the vast majority of CHI member company medical technologies are brought to market. It is a long-standing, proven mechanism that recognizes the oftentimes iterative and incremental nature of medical technology innovation and allows medical device developers to bring new products to market because they are substantially equivalent to existing, or predicate, devices that have already been shown to be safe and effective in actual clinical practice. In the last year alone, over 3,000 new devices were cleared under the 510(k) process, benefiting physicians and the patients in their care.

D. CHI Members are Committed to Patient Benefit through Innovative, High Quality, High Value Added Products

CHI appreciates CDRH's recognition that by "increasing the predictability, reliability, and efficiency of our regulatory pathways, we can help provide better treatments and diagnostics to patients more quickly, stimulate investment in and development of promising new technologies to meet critical public health needs, and increase the global market position of U.S. medical devices."[3] And, as an industry, we share the commitment to improving patient care through innovative, high quality, high value-added technologies.

Given the importance of the 510(k) process, CHI agrees that needed improvements can and should be made to improve upon efficiency, predictability and consistency. And in developing and considering its preliminary reform proposals, we appreciate the attention that CDRH has paid to a process that has provided for stakeholder input and interaction not only through submission of formal written comments, such as these, but through public Town Hall meeting across the country, including California on October 7, and the August 31 webinar.

CHI believes that a substantial number of the Agency's preliminary proposals will indeed improve upon the process, including:

[2] PricewaterhouseCoopers/National Venture Capital Association MoneyTree report, available at https://www.pwcmoneytree.com/MTPublic/ns/index.jsp

[3] Foreword: A Message from the Director. Available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM220782.pdf

- improved staff training on issues such as how to determine whether a 510(k) raises "different questions of safety and effectiveness" and development and assignment of product codes
- revised existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k)
- provision for additional guidance and training for submitters and review staff regarding the appropriate use of consensus standards, including proper documentation with a 510(k)
- enhancement of the third-party reviewer training program and consideration of options for sharing more information about previous decisions with third-party reviewers, in order to assure greater consistency between in-house and third-party reviews
- development of metrics to continuously assess the quality, consistency, and effectiveness of the 510(k) program, and also to measure the effect of any actions taken to improve the program
- working to better characterize the root causes of existing challenges and trends in IDE decision making, including evaluating the quality of its pre-submission interactions with industry and taking steps to enhance these interactions as necessary

Nonetheless, CHI has concerns and reservations about a number the FDA's preliminary recommendations as detailed further herein. We are particularly concerned that, without additional details and careful and thoughtful deliberation and input from all stakeholders, the enactment of a number of the proposals, alone and in combination, may result in a many technologies being unnecessarily and unintentionally relegated into a more complex, complicated and cumbersome Premarket Approval (PMA) or PMA-like clearance process without providing additional patient benefit. In some cases, that increased uncertainty, time and cost will result in product development projects being terminated.

II. PROCESS ISSUES

A. The Reform Process Must be Thoughtful and Specific

Given the length and breadth of CDRH's 200+ pages of preliminary proposals, CHI had requested that the agency extend the comment period to allow stakeholders to more thoroughly evaluate and respond to the complex, multi-dimensional recommendations. While this request was denied, we appreciate that CDRH will consider the views and perspectives provided at the October 7th Town Hall meeting in Irvine, California.

Nonetheless, prior to publication of any final guidance, regulation, or policy change, we urge that FDA go through at least a second round of notice and comment to receive feedback on specific, detailed proposals. Until finalization of any new

guidance or regulations, FDA ought to avoid "informal" adoption of any proposed changes. In addition, FDA needs to make clear which of the proposals the Agency believe could be done via guidance, through rulemaking, or pursuant to statutory changes.

- Specific, Prioritized Proposals Needed: CDRH's proposals lack specificity, which makes it difficult for stakeholders to respond with thorough feedback and definite positions. Simply put, the devil is in the details and, without those details, the best we can do is offer general feedback. Thus, the failure to comment on some proposals does not indicate CHI's support or opposition.
  There is significant value in the FDA soliciting the public's sense of priorities and focusing on a few of them with subsequent, detailed proposals and additional notice and comment. CHI urges the FDA to prioritize amongst its numerous preliminary proposals so stakeholders can provide focused, detailed responses on the likely agency actions. Such prioritization should take into account the key points made by Dr. Shuren in the Foreword to the preliminary proposals and could be done by assigning each proposal to one of three tiers (high priority, medium priority and low priority). Such a process would conserve agency resources, reduce the burden on stakeholders, improve the quality and specificity of proposals and responses, and speed the completion of the 510(k) reform effort. Should the FDA adopt changes without the benefit of meaningful, specific stakeholder feedback on prioritized agency proposals, the results could be devastating, including, e.g., increased costs of production, delayed or denied patient access to products, lost jobs, export of R&D, harm to the economy and adverse impact on the trade balance. As such, subsequent notice and comment on detailed, specific proposals is fundament to the process before acting on any of the general ideas discussed in the Task Force reports. Such prioritization should be made public and be based on actual data. For example, research conducted at the University of Minnesota Law School and by Dr. William Maisel (and presented to IOM) demonstrates the lack of an imminent crisis and also provides data for identifying key issues and leverage points to improve the system.

III. CHI'S DETAILED PERSPECTIVE ON KEY ELEMENTS IN THE CDRH PRELIMINARY PROPOSALS

The 510(k) system must satisfy FDA's statutory mission to advance patient benefit by providing products with a positive risk/benefit ratio and to enhance innovation. This requires predictability, transparency, timeliness, and the avoidance of unnecessary or non-value added burden to patients, providers, industry, or FDA. CHI supports the 510(k) system reform effort, but cautions the FDA not to make change for the sake of change. At the end of this process, the same products currently eligible for 510(k) review should continue to remain eligible. CHI understands that special controls for specific device types for which valid safety concerns have been raised, e.g. infusion pumps, and

AEDs, may be needed, but demonstrated safety issues should be the key basis for any decision to "up-classify" a product.

In considering reforms to the 510(k) process, CHI urges the FDA to recognize risk and benefit calculations and, as required by statute, to balance innovation and protecting public health. The statutory standard set forth by Congress in 21 USC §393(b) is a "reasonable assurance" of safety and effectiveness, not a guarantee. As a policy matter and as set forth by Congress, society has to be able to accept some risk for the sake of greater benefit. Uncertainty is unavoidable, and CHI reminds FDA that the higher threshold of certainty the agency requires, the longer patients wait for innovative, potentially life-saving therapies. Indeed, in some cases, products may never be brought to market. CHI urges FDA to explicitly discuss the impact on innovation in all policy discussions. Training is one – but just one – way for the agency to live out its twin aims of protecting patients and fostering innovation. These twin goals should be explicitly considered, debated, and balanced as the agency prepares to move forward on any proposed reforms.

A. "Indication for Use" and "Intended Use" Should Remain Separate Terms

- Support for Separate Terms: CHI does not support FDA's proposal to combine the terms "intended use" and "indication for use." These terms (which cut across many of FDA's regulatory systems) serve different purposes and reflect substantive differences. While on occasion the terms may be inappropriately switched or misused, overall, these concepts have served well the goal of making available to patients as quickly as possible high quality, safe and beneficial products. Combining these terms will slow innovation by forcing many products into new PMAs and lead to regulatory confusion and review delay, without creating a corresponding benefit to patient safety.
  For example: If going through the FDA today, a scalpel might have a proposed labeling claim saying its intended use was "to cut tissue" and thus surgeons could apply its use to a wide array of disease states and stay within the general labeling. However, to add "indications for use" to the labeling would perhaps add for consideration by the FDA its use in cancer surgery or bariatric surgery. Thus, blurring the line between these phrases could give license to reviewers to interpret this guidance such that the company would be forced to demonstrate a scalpels' clinical benefit as a cancer or bariatric device, rather than simply the more straightforward, yet broad "intended use." This license for misinterpretation would not only stretch the resources of the FDA, but in certain circumstances make it impossible to deliver certain devices to the marketplace – no scalpel manufacturer could afford to study all these indications.
  Also, combining the terms could lead to further healthcare industry confusion as "intended use" is not a term limited to CDRH and devices; it is a term of art used throughout many parts of FDA and the federal Food, Drug and Cosmetic Act

(FDCA). Any change or modification in this definition must be consistent with the broader usage of the term.

Combining the terms "indication for use" and "intended use" will hurt CHI members, disserve patients, and burden the agency, as such a change would:

- push products needlessly into PMAs;
- consume industry and agency resources without evidenced patient benefit;
- add uncertainly, resulting in increased compliance costs, potentially decreased investment and consequent potential job loss; and
- delay or deprive patients access to products.

Simply put, the benefits of combining these terms do not outweigh the harms of doing so.

- Support for Definitional Clarity**:** CHI supports clarifying the definitions of "intended use" and "indications for use" so that such terms may be consistently and appropriately applied by the FDA and industry. Through rulemaking, FDA should define and distinguish the terms "intended use" and "indications for use" based on current statutory definitions and the existing understanding of these terms. These improved definitions should seek to add clarity but should not change or alter the existing definitions of these terms. FDA should ensure that its staff understand these terms and use them appropriately in all regulations, guidance and other written material.

B. The FDA Should Not Create a New Class IIb

- No Statutory Basis: CHI does not support the creation of a new Class IIb. First, we question whether FDA has the statutory authority to create such a new class. Assuming the agency wants to create a Class IIb as a heuristic mechanism to solve some undefined problem, even this is flawed because, regardless of how the change is framed, the result would be the adoption of a new, broad set of requirements that apply across multiple different products, and that is the definition of a class. New classes require statutory authority, and the FDA cannot skirt this requirement by framing Class IIb as something less while accomplishing the same result.
- No Evidenced Need: FDA has not shown that there is a group of 510(k) cleared products that, as a class, require some additional requirements. CHI urges FDA to present data supporting the public health need for such a new classification. Furthermore, the various specific requirements being considered for Class IIb are not value added. There is no showing that requiring Class IIb-wide clinical data would be value added for many products that might be considered for inclusion in Class IIb. Likewise, there is no showing of any need to increase the number of submissions for which clinical data should be submitted.

- Risk of Up-Classification: CHI members are concerned the creation of a new Class IIb might result in products being "up classified" into Class IIb, and/or placing products going through the de novo automatically into Class IIb. This could result in significant and unnecessary delays, hampering innovation which is not outweighed by evidenced benefits for patient safety.
- Support for Risk and Product Specific Special Controls: Rather than creating a new, broad set of requirements that automatically apply across multiple different products, FDA should apply new requirements on a product-by-product basis. First, this is what is required by statute. Second, this is the most effective way to match requirements to products and therefore improve patient safety in an effective, efficient and predicable manner. Broad, automatic requirements based on classification rather than specific risk profiles and product characteristics would disrupt innovation and delay patient access to products, thereby doing more harm to patients than good. CHI recognizes that FDA may, on a case-by-case basis, have reason to demand specific, additional requirements for select products. Recent regulatory initiatives involving special controls for specific device types are an example of how to implement focused, product-specific controls, and this kind of activity should continue if and when specific products are identified which are performing below expectations. However, CDRH's proposal of class-wide special controls is not an appropriate use of special controls and, as such, should, and by statute must, be product-specific.

C. The Scope of 510(k) Eligibility Should Not Be Reduced

- Support for Split and Multiple Predicates: CHI urges FDA to continue to allow the use of split and multiple predicates as both foster innovation and improve patient care, and there is no statutory or regulatory basis for prohibiting or limiting use of split or multiple predicates.
  First, split predicates enable robust product reviews, as information from different areas is considered in the submission examination. Combining already provided technologies facilitates innovation, improves patient care, and permits more efficient delivery of health care. Correspondingly, restricting use of split predicates will slow innovation and increase costs to all stakeholders.
  Second, multiple predicates should likewise not be restricted. In a time of increasing focus on remaining competitive internationally and making the U.S. healthcare system more efficient, the FDA should be encouraging use of multiple predicates to speed innovation and improve efficiency in patient care. CHI recognizes that some improvements for administrative efficiency and predictability might be warranted, but any reform efforts should not have the effect of limiting the number of predicates brought to FDA's attention.
- Support for Revising FDA's Guidance on Product Changes: CHI supports FDA's interest in clarifying the guidance governing product changes to marketed 510(k) products. CHI encourages FDA to revise and update the 510(k) decision tree to

give stakeholders more clarity on when 510(k) applications are appropriate, and when new applications are needed as a result of changes to products or indications. However, flow chart and/or terminology clarifications should not – intentionally or unintentionally – limit the scope of the 510(k) system, or push a substantial number of changes or products from the 510(k) system into the de novo or PMA system. CHI urges FDA to ensure that minor changes in products or uses do not trigger unnecessary submissions.

D. The De Novo Process Should be Logical and Efficient

- Support for a More Effective, Efficient De Novo Process: CHI supports FDA reforms that would make the de novo process more efficient and effective. FDA should ensure data requirements are logical and relevant and that the changes improve timeliness and predictability of review. CHI supports reforms to:
  - allow applicants to begin the de novo process without the necessity of completing the 510(k) (NSE) process;
  - ensure classification decisions are based on legitimate risk assessments and the need to ensure patient access to new products;
  - create defined time periods for key process steps to improve predictability;
  - create a fast track de novo process for obvious Class II products, particularly those of greater patient need;
  - create new regulations or special controls only when required by actual data; and
  - better define the de novo process and clarify the types of products and circumstances that can be handled under the de novo process.
- One Size Does Not Fit All: CHI urges FDA to ensure that any changes do not result in an influx of submissions being subject to de novo review as a result of reviewers finding that products are not exactly the same as the suggested predicate. In addition, in conjunction with other CDRH proposals, products going through the de novo process should not be automatically equated to a PMA or PMA-like pathway or Class IIb (assuming such a class exists). Some de novo products will actually be in Class I. De novo works for some products better than others. For example, diagnostics tend to get de novo review and the system generally works well for them. OIVD should be commended for their application of the de novo process for these products. But while the de novo process may work well for most in vitro diagnostics, that does not mean that the system will necessarily be best fit for implanatables. Quite simply, diagnostics and implantables are two different beasts and one size does not fit all. The de novo process should be tailored to product needs and risks.

E. The Benefit of Mandatory Updates Does Not Outweigh the Potential Burden

- No Evidenced Need: CHI questions the value of mandatory modification updates, labeling updates, and manufacturing processes information. First, longstanding regulation and guidance already sets forth when a submission is needed for some change/update. Any such updates or changes (together with related information) that require the submission of a new 510(k) already must be submitted to the agency for clearance. Second, if the company does not make a submission as required, or the agency disagrees with the manufacturer's determination of whether the change required a new 510(k) FDA can always consider an enforcement action. There are numerous examples of very serious enforcement actions being brought against companies for a failure to submit required modifications. Third, if the manufacturer has made the determination (based on the agency's guidance document) that no new submission is required, FDA has access to information about changes in inspections (generally through the "letter to file" process and in subsequent submissions, and QSR requirements are already in place to ensure that changes are assessed and validated. Finally, FDA has put forth no data to support the notion that new mandatory modification updates, labeling updates or manufacturing information filings would enhance product safety.
- Beware Unnecessary Burden: CDRH generally has no need for this information, as the agency has other ways to obtain it, and thus requiring additional filings adds unnecessary burden on the industry and the agency. A requirement that all modifications be submitted, even as part of a periodic report would burden FDA with insignificant changes and increase the burden on industry for no benefit. At the very least, any new filing obligations must include a de minimis level.

F. Good Manufacturing Practices Should Not be Linked to Product Clearance

- Should Not Link Clearance with GMP: The 510(k) system is entirely independent from the GMP (or, more broadly, the QSR) system. By adding a GMP compliance requirement to the clearance process, the agency is directly undermining and contradicting its stated goal to increase certainty and predictability. CHI opposes any effort to create a "pre-clearance" inspection procedure or requirement. Venture capitalist and other investors will be increasingly leery of investing in a product when QSR or GMP issues could stall clearance for an extended time. It is important to remember that the 510(k) system is a market clearance system, not a manufacturing control mechanism. There may be times in which the party submitting the 510(k) may not be the entity actually manufacturing the device. There is also no data suggesting that the public health would benefit from linking clearance decisions to unrelated GMP/QSR issues. There is also the issue of whether the agency has the statutory authority to deny a clearance because of GMP issues. Unless permitted by statute, the current congressional mandate may not allow this linkage.

- Different Issues with Different Processes: The clearance process and GMP processes seek to answer very different questions, present very different issues, and utilize very different processes and organizations within FDA. These differences raise insurmountable challenges to any direct linkage between manufacturing processes and product clearance decisions. Would any 483 observation be enough to stop a clearance? How recent must the issue be? What if the company indicates that it has been corrected? How material must the issue be? What if the issue relates to a different product within the company? Finally, this proposal raises complex administrative law issues including whether and how the company can appeal any finding of a GMP violation. All in all, this concept creates more issues than it solves.
  Finally, the proposal is seeking an answer to a problem that may not exist. A cleared product that is not manufactured under corresponding GMP requirements may not be shipped. As such, even with a clearance, the company may not, absent some agency agreement, ship such a product in interstate commerce without committing a "prohibited act."

G. FDA Already Has Access to Post Market Information

- FDA has the Authority it Needs (522, 803, 806, etc.): The agency currently has expansive post market data collection systems including, but not limited to, MDR reporting, §522 orders, MedSun, new data mining opportunities with electronic health information, and subsequent submissions. CHI is not aware of any situation in which the agency wanted more post market information and was prevented from doing so by a lack of statutory authority.
- Leverage Existing Data: The more pressing issue for CDRH is not a lack of information or data but rather excessive data. CDRH currently receives 180,000 – 200,000 MDR reports a year. The agency has access to all medical, scientific and engineering publication. CDRH can't currently process all of this data and make sense out of it. CHI suggests that rather than collecting more data (when one can't analyze what one already has), CDRH should focus on high value, high leverage data. The MedSun program is a logical step in that direction. Such focused attention provides better protection of public health and avoids unnecessary burden on the agency, industry and health care providers.

H. FDA Should Not Change Its Approach to Possible Off-Label Use

- FDA Should Not Intrude Into the Practice of Medicine: FDA's proposal to seek statutory authority to permit increased consideration of possible off-label uses in clearance decisions runs afoul of long standing policy and statute. Off-label use is beyond the control of the manufacturer. Assuming that the company is complying with promotional rules, the company cannot control how a physician chooses to use a product. In some cases, off-label use may even be the standard of care. Forcing consideration of off-label use intrudes on physician decision-making and

unnecessarily adds uncertainty, time and burden to the process. It will result in decreased innovation and, importantly, reduced patient access to innovative therapies.

I. CDRH Reviewers and Managers Should Have Enhanced Training

- Training is the key to making any system predictable: CHI supports enhanced training of FDA staff. As the agency has recognized, such training is necessary for robust, value added submission reviewers. Improved science and technology expertise should permit better reviews with less time spent on unnecessary or irrelevant questions. CHI strongly suggests that this enhanced training include interactions and input from all stakeholders. This can include, but is not limited to, industry visits and tours, scientific exchange with industry and others, methods to access industry expertise in an appropriate manner and open forum on emerging scientific topics, developments and issues. CHI hopes that FDA will tap into the vast expertise within industry in California and CHI would be an enthusiastic partner with FDA in developing and providing such training.
- Training is Required on Statutory and Regulatory Requirements: In addition to the technical training discussed above, FDA must ensure that its staff understand and abide by the existing statutory and regulatory structures. As FDA's own material establish, too many FDA reviewers do not understand the statutory limits within which they operate. It is critical that FDA staff understand and follow the statutory and regulatory requirements and boundaries. Too often, companies have been faced with data requests or questions from a reviewer that relates to intellectually interesting but legally irrelevant matters. Such questions and requests delay patient access, add substantial uncertainty to the process and undermine Congressional decisions. Therefore, FDA staff must be training on legal requirements and boundaries and their obligation to act within such bounds whether or not they agree with the Congressional policy.

J. Additional Issues that FDA Should Consider

- FDA already has Rescission Authority: CHI understands FDA's obvious reluctance to permit a fraudulently obtained 510(k) clearance to remain in effect and also seeks authority to prevent future submissions from utilizing such fraudulent submissions. From CHI's perspective, FDA already has the authority to both rescind fraudulent 510(k)s and to eliminate such clearances from further use. 21 USC §513(i), for example, includes provisions setting forth how the agency can legally refuse to permit the use of a fraudulent 510(k). Any such enhanced rescission authority must be carefully considered to avoid unintended consequences on subsequent submissions that innocently utilized the now suspect clearance. This is an example of a concept that requires specific detail before any stakeholder can express more than very general views.

- Trade Secrets and Confidential Information Must be Protected. CHI is generally supportive of CDRH's recommendation that submissions include photos and schematics that would be helpful to the review process, but such material must be for internal FDA-use only and not be made public. Otherwise, highly valuable trade secrets and confidential business information will be irreparably damaged. Any minimal value of such public disclosure is vastly outweighed by the risk to confidential information. Remember that once public, such information can be used in any way in any jurisdiction, including for products made and sold outside of the US.

IV. CONCLUSION

CHI supports robust FDA and regulatory systems that provide innovative, and safe and effective products to patients. We appreciate this opportunity to share our comments on the Task Force proposals and will look forward to future opportunities to engage with FDA on improving the 510(k) process.

Todd E Gillenwater
Vice President, Public Policy

AMS
Solutions for Life

American Medical Systems
10700 Bren Road West
Minnetonka, MN 55343

Phone: 952-930-6000
Fax: 952-930-6157

October 4, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: CDRH – Volume I: 510(k) Working Group Preliminary Report and Recommendations

Dear Sir/Madam:
American Medical Systems (AMS) appreciates the opportunity to comment on the *CDRH – Volume I: 510(k) Working Group Preliminary Report and Recommendations*. AMS is a leader in medical devices and therapies to treat urological and gynecological disorders. Our solutions address male and female urinary incontinence, erectile dysfunction, prostate disorders, urethral strictures, pelvic organ prolapse and fecal incontinence. Although not life-threatening, these disorders greatly affect quality of life and social relationships.

AMS supports the overall goals of the FDA of providing a consistent and transparent review process, ensuring marketed devices provide a reasonable assurance of safety and effectiveness, and fostering innovation in the medical device industry. AMS agrees that the report presents some much-needed improvements to the 510(k) process. Specifically, AMS strongly supports streamlining the *de novo* 510(k) process and bringing additional clarity to the standards, guidance documents and definitions used by FDA. These changes have the potential to provide greater transparency and predictability to the 510(k) process.

At the same time, AMS is concerned that several of the recommendations of the 510(k) Working Group could significantly impact the development and clearance and patient access to important medical technology of devices, creating significant barriers to innovation while not achieving commensurate benefits to the public health. For example, restricting the use of multiple or split predicates would unnecessarily limit innovation by forcing novel devices to a PMA pathway and causing the sponsors to reassess the business case for the product. Similarly, the creation of a Class IIb subset would unnecessarily slow the review process and create overly burdensome restrictions to achieve clearance of those devices. This is in direct conflict with the least burdensome approach requirements and the additional costs and time to market would result in less innovation and higher costs to the healthcare system.

AMS believes that the cumulative effect of the more than 70 CDRH proposals in the two reports would result in a revolutionary change to both the 510(k) process and in the larger regulatory framework. Implementing such changes piecemeal will result in confusing and ever-changing standards and negatively impact bringing new devices to market as manufacturers try to identify and comply with all of the new requirements that will be required at the time they submit their device for clearance.

AMS strongly suggests that FDA reevaluate whether this vast number of changes is necessary to further the advancement of patient care. AMS believes that the 510(k) program has been proven as an effective paradigm for placing devices on the market for over 30 years. If such a large number of significant changes are truly required, FDA should follow the pathway of other significant changes, such as the implementation of the QSR, and implement the new process in its entirety rather than on peicemeal basis.

I. Modification to Existing Guidance on when to Submit a 510(k) and Periodic Updates on Device Modifications

Due to the wide range of devices regulated by the 510(k) process and the varying types of potential changes to those devices, the existing flow chart is not always applicable to all devices and device changes. Modification to the guidance may help clarify when a 510(k) is required, gaining alignment not only within the industry but also within CDRH. This would result in more consistent submission of new 510(k) for significant changes to a cleared device. The guidance updates should focus on determination of relevant changes and their impact on the safety and effectiveness of the device.

AMS is unclear as to the FDA's basis for proposing periodic reports of all changes to cleared devices. There was no data presented as to the rate of safety hazard due to unreported changes to 510(k) devices. Devices subject to the pre-market approvel (PMA) regulations already have such requirements, and no data was presented to establish that there are fewer recalls or safety incidents related to design changes for those devices compared to devices cleared via 510(k)s. Thus, AMS is concerned that the requirement for periodic submittal of notifications will be burdensome to industry and FDA, with no benefit to the health of the general public.

It is the responsibility of the 510(k) holder to evaluate modifications to determine whether they require submission of a new 510(k). FDA guidance currently states that a 510(k) for a device change should incorporate all the changes to the device subsequent to the original submission, and the new 510(k) should contain data comparing the new device to the legally-marketed device. This mechanism, if consistently enforced, provides the Agency sufficient information about changes to 510(k) devices. Additionally, changes to 510(k) cleared devices are subject to the design controls sections of the Quality System Regulation and may be routinely reviewed in the course of an FDA inspection. Additional requirements for submission of modifications would be burdensome to industry and would consume significant resources in CDRH or OC in the submission and review process. Based on the information provided, it does not appear that this would be a wise investment of FDA's limited resources.

Sending periodic updates of device modifications or narrowing the scope of the Special 510(k) could slow the process of implementing minor, but beneficial modifications to marketed devices. The Special 510(k) process has been an efficient and effective mechanism for submitting notification to CDRH of device modifications and has encouraged submission of design changes. The manufacturer's certification to design controls ensures that appropriate processes have been

followed for assessing the significance of device changes and provides FDA with an adequate enforcement mechanism.

II. Submitting Detailed Photographs or Schematics

While providing detailed photographs and schematics of a device under review may in some cases allow CDRH review staff to develop a better understanding of the device's key features, it is important to note that at the time of 510(k) submission, the final production version of the device may not be available. When required for clarity to the review process, it would be appropriate that CDRH request a photograph or schematic of the device under review as a means to aid the review process.

The FDA also proposes that the detailed photographs or schematics be included in the publicly-available 510(k) database. AMS strongly opposes this concept. While general photographs containing published information may be suitable to place in a public database, detailed photographs and schematics often contain proprietary engineering information and should not be made publicly available. In the interest of protecting proprietary information domestically and internationally, at the very least, a redacting process must be in place prior to the publication of schematics, detailed photographs, or any proprietary information. FDA's stated reason for this suggestion was to "make it easier for manufacturers to identify appropriate predicates and predicate information." However, it is inconsistent with the principles of protection of confidential, proprietary information for a federal agency to use the data from one company to make it easier for their competitors to enter the market.

It may be helpful for reviewers to have access to at least one unit of a device during the review process, particularly for complex products or those with complex descriptions. It is important to note, however, that keeping a device available indefinitely so it can be examined when it is cited as a predicate is impractical and would provide limited benefit, as device characteristics often change after passing their labeled shelf life. Additionally, the device under review may not be a product of the standard manufacturing process, as production process validation is not required to be completed prior to submission of a 510(k). AMS suggests that providing a sample device during the review be treated as a CDRH *request* and not a *requirement*.

III. Disallowing the Use of Split Predicates and Appropriate Use of Multiple Predicates

In its recommendation, FDA proposes disallowing the use of split predicates and restricting the use of multiple predicates. AMS opposes this recommendation and believes that FDA should continue to permit split and/or multiple predicates under the 510(k) process. Both split and multiple predicates have proven to be a valuable tool to provide an appropriate, risk-based level of regulatory control for devices that do not have a single established predicate, but whose risks do not warrant expending the resources of the sponsor or the FDA to navigate the PMA regulatory pathway. When establishing requirements for the use of a split predicate, (using one predicate as the basis for a comparison with the same intended use and another predicate as the basis for a comparison with respect to technological characteristics) the risk management process should be incorporated into the review process for evaluation of substantial equivalence. Often,

the technological risks are well characterized in another indication and the risk management process can accurately identify both the risks and the appropriate risk-control mechanisms for the device. Information from such risk management systems should be leveraged to understand complex devices that require the use of split predicates, rather than disallowing this important tool in all situations.

The report cited a concern with the use of multiple predicates due to the rate of MDRs, injuries, malfunctions, and deaths in devices that had used multiple predicates. However, the data discussed demonstrated that in submissions with fewer than five predicate devices, compared to one predicate device, there was no increase in reported deaths or malfunctions, and only a very slight increase (0.03%) in MDRs and (0.05%) in injuries. Based on the data, AMS supports FDA's recommendation that multiple predicates be limited to fewer than five.

As devices become more complex and contain more features, disallowing the use of split or multiple predicates will limit innovation and discourage the addition or combination of proven technology into medical devices with an established safety/risk profile.

IV. Creation of Class IIb Device Subset

AMS is very concerned about the recommendation that CDRH develop a subset of class II devices ("class IIb") particularly because other sections of the Working group recommendations imply that this "subset" would be subjected to requirements that diverge from the concept of "substantial equivalence" and the principles of "least burdensome" and move toward the safety and effectiveness standard established for PMA devices. Examples of this divergence include recommendations that this subset of devices require the submission of clinical study data and manufacturing information. If implemented, medical device innovation would be significantly slowed by subjecting certain Class II devices to more stringent regulatory requirements similar to that of a premarket approval process.

The decision to require the submission of manufacturing information and clinical data should be based on the scientific evidence and risk management activities, including the risk analysis and proposed mitigations. The risk management process, through the use of ISO 14971:2009, encompasses the product life-cycle and identifies the level of risk and mitigation in all aspects of the device. This includes monitoring data about the device and similar devices and updating the risk management documents and mitigations when needed. Defining a subset of devices as "high risk", without examining the safety profile and risk mitigations put in place for the individual device, would unnecessarily slow the delivery of well characterized devices to the target patient population.

By definition, Class II devices are subject to Special Controls. FDA should leverage this mechanism rather than creating a new class of devices that makes it difficult for devices with a proven safety/risk profile to reach patients. The Special Controls authority could be used to require submission of detailed risk management documents for a specific device category, such as the risk management plan, risk management report and detailed risk analysis. This information could then be used to understand whether the data included in the 510(k) is sufficient or whether additional data, such as clinical data, is required. This would allow additional information to be

requested for devices that have increased risks, while avoiding adding burdensome data requirements on well-characterized categories of devices.

Requiring the submission of clinical and manufacturing information for 510(k) clearance for large segments of medical device categories would defeat the purpose of the 510(k) program, causing a potentially lengthy and burdensome process, similar to that for PMAs, and ultimately hindering device innovation.

V. Strengthening the *de novo* Process

AMS supports the recommendation to strengthen the *de novo* process. Strengthening and optimizing the *de novo* process will benefit CDRH, industry, and patients. AMS recommends implementing a risk-based approach that would allow some products that are currently subject to PMA for the sole reason that no suitable predicate exists to be more efficiently and effectively reviewed through the *de novo* process.

To achieve the goal of a more transparent and efficient de novo 510(k) process, AMS recommends that FDA eliminate the need to submit a 510(k) and receive an NSE determination before requesting *de novo* down-classification, so that submission of a *de novo* is a "one-step" process, rather than the current two-step process.

VI. Implementing a Uniquie Device Identifier (UDI)

AMS is concerned that FDA mistakenly views UDI as a panacea for problems with the current system for monitoring medical device safety data, and has not fully considered the potential impacts of such a system. For instance, requiring that a UDI be integrated into some types of devices, such as nanotechnology or some types of implants, would be technically challenging and very expensive. In some cases it may require significant design changes be made in order to avoid creation of new safety risks. Additionally, it is unclear how FDA's implementation of UDI will address multi-component devices, which can be assembled into a variety of final configurations to form the finished device, particularly if there are iterations to some of these components but not others.

It is also unclear how the use of the UDI will provide better safety data than is currently available. The primary limiting factor to the currently reported data is not the inability to identify relevant related devices, but the significant under-reporting of events by user facilities, coupled with a database structure that makes it difficult for those who want to present such information in a submission to compile and analyze data.

VII. Additional Rescission Authority

FDA has numerous tools to remove violative devices from the market and should not implement a process that may broadly limit access to safe and effective medical devices. FDA currently has authority to enforce postmarket actions including reclassification, recall, warning letters, seizures and other actions. If a device is considered unsafe because it is manufactured under noncompliant GMPs, is manufactured incorrectly, or the manufacturer has unlawfully changed

the design without meeting the appropriate premarket requirements, the conditions must be remedied. However, these conditions are not related to the safety and effectiveness of the device design, which was the subject of the 510(k) clearance and thus are not grounds for revoking the original 510(k) decision.

Section 516 of the FD&C Act provides for the banning of a medical device in situations of substantial deception or unreasonable and substantial risk of illness or injury. Banned medical devices can no longer be legally marketed and could therefore not be cited as a predicate device. FDA also has the authority to issue an order for mandatory device recall as specified in Section 518 of the Act or reclassify a device as specified in Section 513(e) of the Act. FDA also may, when necessary, obtain court orders for product seizure. These tools enable the Agency to protect the public health and maintain the integrity of the classification system.

If a device clearance is rescinded for reasons unrelated to safety and efficacy of the technological characteristics of the device, it could result in other devices that have used that device as a predicate being rescinded as well, with potentially significant negative impact to public health. As noted above, FDA currently has the tools to isolate a device that violates any part of the Act without creating unreasonable jeopardy for innocent parties.

In closing, AMS appreciates the opportunity to provide comments on the proposed changes to strengthen the 510(k) process. If you have any questions regarding these comments or if you would like additional information, please contact me at (952)930-6000

Sincerely,

Ginger Glaser
Senior Director, Global Quality
American Medical Systems

October 4, 2010

Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2010-N-0348: Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations; Availability; Request for Comments

The undersigned organizations appreciate the opportunity to comment on the 510(k) Working Group's Preliminary Report and Recommendations.

As groups representing the medical technology industry in our respective states, we have a standing interest in encouraging the development of new treatments and cures and in assuring that medical products are safe and effective. We applaud FDA for its efforts to conduct an in-depth examination of the 510(k) process and for the extensive work and data collection that went into the preliminary report. We are pleased to support several of the FDA recommendations, which we believe will result in a more predictable and consistent process that will help support product innovation and will provide greater assurance to the safety and effectiveness of cleared devices. At the same time, however, we are concerned that many of the recommendations in the report, if implemented, will result in a more burdensome and time-consuming approval process that will discourage development of new treatments, delay availability of improved products to patients and providers and interfere with physician and other health care providers' clinical decision making.

The recommendations of the report must be considered against a backdrop of several key facts. For most products, the 510(k) process has an exemplary record of assuring safety. Studies by the Battelle Memorial Institute, Professor Ralph Hall of the University of Minnesota and Dr. William Maisel of the Medical Device Safety Institute at the Beth Israel Deaconess Hospital in Boston, all show an extremely low recall rate of marketed products, and only a fraction of recalls are due to problems that might conceivably have been identified in the review process.

Recent FDA data shows disturbing trends in the 510(k) process, which result in delays and frustration for manufacturers, providers, and patients alike. Treatment of submissions is less predictable and consistent and both total review time and the time manufacturers spend answering FDA questions about submitted applications have increased substantially. The number of submissions withdrawn has grown significantly, suggesting that FDA requirements have become less clear or new requirements have been arbitrarily applied. Most disturbing, from the point of view of our member organizations, is that manufacturers are more frequently introducing innovative new products in Europe first, delaying access by American patients to treatments and cures by months or even years.

Key recommendations we believe will improve the 510(k) process include proposals included in the "continuous quality assurance section of the report." We believe enhancing the training, professional development, and knowledge-sharing among reviewers and managers, as proposed in this section of the report, is critical to addressing the problems described above as well as assuring the products cleared through the process are safe and effective. We believe the theme expressed throughout the report that FDA should develop more guidance documents would be a significant step forward. Good guidance documents are very important to ensure consistency of reviews. We also believe the FDA proposal to simplify and improve the "de novo" process for products that are too novel to meet the normal 510(k) "substantial equivalence" test but not risky enough to merit review through the PMA process would be very constructive.

We are also supportive of the general concept of applying special requirements to a small subset of devices. While some the specific requirements discussed in the report may be overly burdensome, the concept of applying special, clearly defined requirements to a small number of types of devices where enhanced premarket and postmarket requirements are appropriate to demonstrate safety and effectiveness is a good one that would both improve FDA's ability to protect the public and provide manufacturers with clear requirements that would need to be fulfilled to get a product of this type cleared. Effective implementation of this recommendation would obviate any need for many of the sweeping changes FDA has proposed to the process, since for the vast majority of device types, the current system is fully effective to assess safety and effectiveness.

While the recommendations above are constructive, we are very concerned about the bulk of the recommendations contained in the section entitled "A Rational, Well-Defined and Consistently Interpreted Review Standard." We believe that redefinition of the term "substantial equivalence" and potential new limitations on acceptable predicates, as well as eliminating the separate classification of intended use and indications for use go to the heart of the current program and have the potential to make approval more time-consuming and to reduce innovation. We are concerned that the proposal to give FDA new authority to consider an off-label use when determining the "intended use" of a device under 510(k) review could negatively impact patient care. Withholding clearance of a technology because the agency believes it may be used for an off-label purpose not sought by the sponsor could prevent technologies from reaching patients in need.

We are concerned that, taken as a whole, the recommendations in the report, if fully implemented, would represent a huge diversion of FDA resources without commensurate gain as well as possibly push technologies that appropriately go through the 510(k) process to go through the Premarket Approval (PMA) process, unnecessarily driving up research costs and delays in patient access.

The process of retraining staff and implementing new procedures and definitions throughout the program poses a real danger of dramatically slowing FDA's approval process and discouraging innovation over an extended transition period. We urge that changes be phased in and that they be limited to those where there is a clear and demonstrated need that requires corrective action.

In assessing every change included in the report, it is vital that the interests of the medical technology industry be represented and that prompt access to new treatments and cures be a key consideration. Changes that may jeopardize that goal should not be made unless there is clear evidence that the changes are necessary to address a demonstrated public health problem.

Thank you for considering these comments.

Sincerely,

BayBio
BEACON: Biomedical Engineering Alliance Consortium
BIOCOM
BioOhio
CHI-California Healthcare Institute
Colorado Bioscience Association
Florida Medical Manufacturers Consortium
HealthCare Institute of New Jersey
Massachusetts Medical Device Industry Council
Medtech
MichBio
Pennsylvania Bio
Texas Healthcare and Bioscience Institute

MEDICAL DEVICE MANUFACTURERS ASSOCIATION
Innovation Today for Better Health Care Tomorrow™

1350 I Street, NW
Suite 540
Washington, DC 20005
P: (202) 354-7171
F: (202) 354-7176
www.medicaldevices.org

October 4, 2010

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2010-N-0348: "*Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations*"

Dear Sir or Madam:

The Medical Device Manufacturers Association ("MDMA") appreciates the opportunity to comment on the preliminary recommendations included in the U.S. Food and Drug Administration's ("FDA's") two preliminary reports released on August 5, 2010 entitled, *510(k) Working Group Preliminary Report and Recommendations,* and *Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations*.[1] MDMA is a national organization representing hundreds of innovative, entrepreneurial medical technology companies. MDMA's mission is to ensure that patients have access to the latest advancements in medical technology, most of which are developed by small, research-driven medical device companies. As such, MDMA supports FDA's commitment to exploring meaningful, predictable and transparent means of improving the premarket notification process and incorporating new science into regulatory decision-making in a manner that fosters innovation, encourages advances in science and medicine, and focuses on the public health.

MDMA appreciates that FDA is engaging in this ongoing dialogue regarding the regulation of medical devices. Indeed, history demonstrates that, when FDA and industry work in a constructive and collaborative manner, patients benefit from the results. MDMA is optimistic that, through continued interactions with industry, including the small, entrepreneurial businesses that predominately characterize the medical device industry, FDA will implement reforms that improve the premarket review process by making it more predictable, transparent and reasonable. In the end, this will serve FDA's dual goals of providing patients with timely access to safe and effective medical therapies and promoting innovation. For instance, FDA should address the challenges imposed on industry by vacillating review goals and inconsistently applied standards, which stifle medical device innovation and are ultimately detrimental to the public health. Further, certain unpredictable regulatory requirements result in confusion, which can unnecessarily delay product clearances and approvals, resulting in increased time to market, and ultimately a delay in patient access to potential lifesaving therapies. Therefore, MDMA

[1] 75 Fed. Reg. 47307 (Aug. 5, 2010).

supports FDA's efforts to provide greater clarity where confusion may currently exist among its review staff.

Indeed, in many instances, providing review staff with additional training on current regulations and requirements, and empowering managers to effectively administer the premarket review process, are more effective ways to enhance the predictability and efficiency of the process than implementing fundamental changes to the underlying process itself. As noted by two independent studies presented before the Institute of Medicine ("IOM"), the 510(k) process has historically been an efficient and effective mechanism to provide patients with timely access to safe and effective products.[2] Therefore, it is imperative that, as FDA contemplates specific changes to the 510(k) process, it can rely on valid scientific evidence to support that these specific changes are warranted. FDA also has the burden to demonstrate, through valid scientific evidence, that the proposed changes to the process would correct a specific deficiency in the current program and would not compromise patient care or innovation. MDMA respectfully submits that a brief survey of FDA reviewers is not adequate to support many of the recommendations included in the preliminary reports.

MDMA recognizes that these two reports are preliminary and that FDA's Center for Devices and Radiological Health ("CDRH") has not made any decisions on which specific recommendations to pursue. Given the preliminary nature of these reports and the fact that many of the proposals lack the necessary specificity to provide detailed responses, we appreciate CDRH's commitment to provide stakeholders with multiple additional comment opportunities before FDA moves forward and implements any changes to the premarket review process.[3] To enhance the quality of feedback received by stakeholders, FDA should provide specific details on each recommendation, including: scientific data (not anecdotes) to support the changes, evidence that the proposed changes would address the underlying deficiency, and a proposed strategy on how FDA anticipates implementing the changes. This strategy would include FDA prioritizing the changes it would like to pursue. In addition, before moving forward with final implementation of any changes, FDA must assess the costs to the government and to industry related to any modifications. Taking this comprehensive approach to the review process will permit stakeholders with the opportunity to provide more specific responses to each of the proposals and provide greater clarity on how FDA intends to proceed.

Below please find MDMA's preliminary comments on the recommendations included in the two reports. Given the overwhelming number of proposed changes and the limited information about how these changes would be implemented, it is difficult to address all of the issues contained in the reports. Thus, MDMA has limited its comments to only certain key recommendations, and failure to comment on a specific issue should not be viewed as support by MDMA.

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[2] R. Hall, "Using Recall Data to Assess the 510(k) Process," IOM Public Meeting, July 28, 2010, available at http://www.iom.edu/ /media/Files/Activity%20Files/PublicHealth/510kProcess/2010-JUL-28/06%20Hall.pdf; W. Maisel, "Premarket Notification: Analysis of FDA Recall Data," IOM Public Meeting, July 28, 2010, available at http://www.iom.edu/ /media/Files/Activity%20Files/ PublicHealth/510kProcess/2010-JUL-28/05%20Maisel.pdf.

[3] CDRH Webinar, August 31, 2010.

In general, MDMA supports the following recommendations and concepts that will improve the predictability of the 510(k) process.

Enhanced training of review staff, including managers. MDMA supports enhanced training, professional development, and knowledge-sharing among reviewers and managers, in order to support consistent, high-quality 510(k) reviews. Based on feedback from MDMA's members, medical technology companies continue to experience wide variation in reviewer expertise, as well as variation among reviewers who follow FDA's Interactive Review Guidance and those who do not.[4] As noted above, when FDA and industry collaborate throughout the premarket review process, the process is more efficient and effective.

Improving the 510(k) summary process. MDMA supports the recommendation to issue guidance and SOPs for the development of 510(k) summaries to assure they are accurate and include all required information identified in 21 C.F.R. 807.92. The development of guidance documents should include an opportunity for industry to comment. In addition, MDMA supports the creation of a standardized electronic template for 510(k) summaries that would be posted on CDRH's website. While these summaries would not include proprietary information, if accurate and consistent with the requirements of the regulation, they would be an extremely useful tool to assist companies in determining appropriate predicates.

In addition, these summaries would provide industry with timely access to CDRH's current regulatory expectations and requirements for specific product categories. MDMA believes that this would obviate the need for the "Notice to Industry" proposal recommended in the report. MDMA is concerned that issuing "Notices to Industry" would undermine the protections included in FDA's Good Guidance Practices.

Enhanced IT and database infrastructure. MDMA also supports FDA's efforts to enhance its IT and database infrastructure to better manage the premarket review process. As part of these efforts, FDA should utilize metrics to identify product areas that may require additional resources or reviewers in need of further training. For example, if the database tracked a reviewer's daily activities consistently throughout the year (instead of the current practice of two-week "spot checks" six times a year), FDA could identify certain trends related to specific product types, including those that take longer to review than others. Such product areas may be ideal candidates for additional FDA guidance to provide greater clarity regarding regulatory and other requirements for CDRH and industry. In addition, this tracking system could enable FDA to identify issues related to a specific reviewer, who may benefit from additional training or mentoring from a senior reviewer. Such information would only be used by CDRH management and the Center Science Council to enhance the predictability and consistency among reviews, and would not be made public.

Creation of public metrics and assessments. MDMA supports the creation of public metrics and assessments to continually assess the quality, consistency and effectiveness of the 510(k) program, and also to measure the effect of any actions taken to improve the program. These metrics should be developed through a transparent process that incorporates the input of all affected stakeholders.

[4] FDA Guidance, "Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements," February 28, 2008.

Third-Party Review Program. MDMA strongly supports the continuation of the Third-Party Review Program.

Transfers of 510(k) ownership. MDMA supports the recommendation that CDRH develop guidance and regulations regarding appropriate documentation of transfers of 510(k) ownership.

MDMA considers the following recommendations to be potentially helpful in making the premarket review of medical devices more predictable and transparent, however, MDMA requires additional details regarding these proposals in order to appropriately determine their ultimate impact.

De novo classification process. MDMA supports efforts to revise existing guidance to streamline the current implementation of the de novo classification petition process and clarify FDA's evidentiary expectations for de novo reviews. These efforts should include developing rational data requirements for new class I or II devices. Further, any modifications to the process should recognize that, because de novo classification petitions are filed after a determination through a 510(k) submission that a device is not substantially equivalent, this process should remain an appropriate pathway for devices. Companies must continue to be able to utilize multiple predicates to demonstrate substantial equivalence. In those instances where a predicate does not exist, or the device has a new intended use or a new technology that raises a different question, and the risk profile does not rise to class III, a timely and predictable de novo process will enhance patient, consumer and health provider care and promote innovation. This process would include defined time periods for key process steps. It would also include "fast-tracking" the process for obvious class II products. These changes would improve this process for patients and innovators.

Creation of the Center Science Council. The establishment of the Center Science Council ("Council") is an interesting concept and has the potential for ensuring consistency among reviewers and managers. The Council could serve as a body to better assess the quality and training of staff and review data related to the performance of branches and reviewers to ensure continuity and consistency across CDRH. Furthermore, companies are frustrated when disputes arise between outside clinical experts and CDRH clinical experts over scientific questions, including clinical trial design. If the Council provided a forum for industry to address these disputes in a timely and objective manner, this would further enhance the predictability and transparency of the premarket review process – particularly if reviewed during the "pre-IDE timeframe." To ensure a proper base of knowledge, the Council should partner with "clinical centers of excellence" with experience in medical technology engineering and relevant clinical and scientific expertise to provide well-informed and science-based input to CDRH. In addition, the Council should include participation and input from physicians, inventors and industry. The Council should not include input from anonymous or confidential sources, or groups without specific scientific or engineering expertise. Also, the Council should not be used as a mechanism to overturn decisions already made by FDA. MDMA looks forward to receiving additional details regarding the proposed Council, including the process for handling premarket disputes internally and externally, the factors that prompt the Council's involvement, a transparent and clear pathway through which the Council would function, and the inclusion of industry experts to participate in the process.

As it relates to the issue of addressing "new" science, it is vital that the Council include external experts such as practicing physicians, industry and engineers in the specific area of "new" science FDA is exploring. As MDMA has stated in previous FDA comments, in determining "new scientific information," FDA should hold potentially relevant information to the same standard of "valid scientific evidence" that it employs in the approval process.[5] For example, one peer-reviewed journal article or a pattern of Medical Device Reports ("MDRs") would not necessarily constitute "new" science. Lancet's recent retraction of a journal article linking vaccines to autism is a clear example of the negative impact of making decisions without robust data and information.

MDMA strongly opposes the following recommendations. Based on the feedback from MDMA members, these changes would create more uncertainty and additional costs, and impede the ability of emerging companies to provide patients with timely access to safe and effective products.

Consolidation of the terms "indication for use" and "intended use." MDMA strongly opposes the recommendation to consolidate the concepts of "*indication for use*" and "*intended use*" into a single term "intended use." According to the report, the justification for the change was based upon a "survey" of CDRH review staff, some of whom expressed confusion over the two terms. Rather than merging the two terms, CDRH should take the necessary steps to educate its staff on the meanings of the two different concepts. "Intended use" is defined as the "objective intent of the persons legally responsible for the labeling of the devices" and encompasses all aspects of how and for what purpose and under what circumstances the device is intended to be used.[6] An "indication for use," in contrast, has a very precise structure and precise meaning for the product. As defined in FDA regulations, "indication for use" includes "a general description of the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended."[7] Indications for use are listed on the labeling of a device and may or may not depict a device's entire intended use. Intended use, on the other hand, is a regulatory concept that determines whether a product must proceed through the 510(k) pathway or the PMA pathway,[8] and gives FDA considerable discretion in the regulation of product labeling, promotion, advertising and device design. Given that new indications for use that are within the same intended use can utilize the 510(k) pathway and a "new" intended use would require a PMA, or de novo petition, consolidating the two terms could dramatically alter the number of products that would be permitted to utilize the 510(k) pathway. Since 1976, most new indications for use have been determined to have the same intended use and have entered the market through the 510(k) review process, unless the new indication was determined to be a "new" intended use, in which case a PMA was required. Furthermore, given the number of

[5] MDMA's comments to Docket No. FDA-2009-N-0575, "Incorporation of New Science Into Regulatory Decisionmaking Within the Center for Devices and Radiological Health, Public Meeting," February 24, 2010.

[6] 21 C.F.R. "801.4.

[7] 21 C.F.R. "814.20(b)(3)(i); FDA 510(k) Memorandum "K97-1, "Deciding When to Submit a 510(k) for a Change to an Existing Device," January 10, 1997.

[8] FDA 510(k) Memorandum "K86-3, "Guidance on the CDRH Premarket Notification Review Program," June 30, 1986.

guidance documents and regulations that reference "indications for use," eliminating this concept would have a cascading impact that would fundamentally impact the 510(k) program overall.

Creation of a "class II(b)" designation. MDMA also strongly opposes the preliminary recommendation to create a "class II(b)" designation for higher-risk class II products. The proposal includes generic descriptions of the devices that may fall within this designation, such as whether a device is implantable. Such a proposal has the potential to impose automatic requirements based on classification rather than the specific risk profile of the product under review. If FDA deems a product to have demonstrated a safety or effectiveness issue, FDA currently has the authority in the 510(k) process to require additional information regarding that specific product's risk profile.[9] MDMA supports the continuation of this case-by-case approach using valid scientific evidence. As mentioned previously, two independent studies have demonstrated that the current 510(k) review process has been extremely effective in protecting patients, consumers and health care providers. The evidence does not support the creation of a new "class II(b)" category of medical devices for higher risk products. Indeed, in the 1990s, FDA implemented a three-tier system that ranked medical devices according to the intensity of required review and discontinued the program after a few years because it proved unworkable. Moreover, creation of a new class of medical devices cannot be accomplished without amending the Federal Food, Drug and Cosmetic Act ("FDCA").

Pre-Clearance Inspections. MDMA does not support pre-clearance inspections for devices undergoing 510(k) review. Such a requirement would delay a product's entry into the market for reasons that may be unrelated to its safety and effectiveness, and add uncertainty to the product development process. Furthermore, FDA's review of a manufacturing facility's compliance with Good Manufacturing Practices involves a different analysis than the clearance of a product through the 510(k) process, and is a separate General Control under the FDCA, and FDA should not confuse the two. Finally, a requirement for pre-clearance inspections is unnecessary since FDA can inspect a company at any time under existing authority.

Level 1- "Immediately in Effect" guidance documents. FDA should refrain from issuing Level 1- "Immediately in Effect" guidance documents. The process used to issue these guidance documents undermines Good Guidance Practices and is also inconsistent with FDA's transparency initiative. Furthermore, the issuance of these guidance documents creates less predictability and does not foster collaboration between FDA and industry.

Statutory amendment to consider off-label uses. MDMA opposes the recommendation that CDRH pursue a statutory amendment to section 513(i)(1)(E) of the Federal Food, Drug, and Cosmetic Act that would provide FDA with express authority to consider an off-label use, in certain limited circumstances, when determining the "intended use" of a device under review through the 510(k) process. Such a modification would improperly extend FDA's authority into the regulation of the practice of medicine.

Multiple predicates. Although much attention has been given to the utilization of predicates, there has been no valid scientific evidence to demonstrate that utilizing multiple predicates is inappropriate or results in patient harm. The ability to rely upon more than one

[9] 21 C.F.R. §860.7.

predicate device to demonstrate the substantial equivalence of a new device that combines attributes of two previously cleared devices is absolutely essential to innovation. Additionally, many medical devices are systems composed of several different individual devices connected by software. It is essential that these device systems use more than one predicate to demonstrate substantial equivalence in their 510(k) submissions. Without this ability to build on prior technology and uses under the 510(k) process, device manufacturers would be limited to recreating the same medical device repetitiously or pursuing approval of a PMA. It could also force manufacturers to submit multiple 510(k) submissions in order to use more than one predicate in order to receive a timely review. Requiring the additional, and potentially unnecessary, data required to support a PMA application could render the cost calculation for the device prohibitive. Furthermore, it is a waste of FDA's valuable and limited resources to apply a more rigorous level of scrutiny when the additional scrutiny is unnecessary to establish that the devices provide reasonable assurance of safety and effectiveness. Therefore, MDMA opposes any attempts to limit the number of predicates a company can use in a 510(k) premarket submission.

Rescission authority. Although MDMA supports clarifying FDA's authority to rescind a 510(k) clearance in the case of fraud that is material to a determination of substantial equivalence, FDA should not be granted broad rescission authority. If FDA is concerned that a company would rely upon an unsafe or ineffective product for its 510(k) submission, FDA should deem the predicate product misbranded and thereby prevent the product from being marketed and used as a predicate.[10]

Demonstration models. Some of the proposed recommendations would add significant costs and burden to industry without any corresponding improvement to safety, effectiveness or innovation. One of these recommendations includes a requirement that companies keep a demonstration model at their facility. Aside from the costs associated with this requirement, a company is not required by law to manufacture a product or to even have a manufacturing facility in order to gain clearance for a product. Rather, MDMA supports FDA's existing authority under 21 C.F.R. 807.87 to require submission of engineering drawings and photos of the proposed device under review, and even submission of videos or samples may be appropriate. Such materials should be used for internal purposes only, since public disclosure of these materials could enable others to copy the technology, which could adversely impact companies. Further, the Quality System Regulation requires that companies maintain documentation of the design of the device and any changes to that design.[11]

Reporting device modifications. While MDMA supports revising existing guidance to clarify what types of modifications FDA believes warrant submission of a new 510(k), requiring all device modifications to be reported to FDA would be overly burdensome to both industry and FDA. Such reporting is also unnecessary because FDA currently has access to this information during FDA inspections. Furthermore, FDA's 1997 guidance on changes or modifications to a 510(k) device requests that companies submitting a new 510(k) for a modified device include any modifications they have made to their device since their last 510(k)

[10] FDA should take such action if it determines that a product is unsafe or ineffective with regard to its design or use, and not where a product is out of compliance with applicable manufacturing requirements.

[11] 21 C.F.R. 820.30.

submission in order to ensure that the reviewer understands the device under review as compared to the firm's own predicate device.

Creation of an "assurance case" framework. MDMA opposes the adoption of an "assurance case" framework for 510(k) submissions. FDA should use the processes for risk analysis set forth in existing ISO 14971 and the Quality System Regulation rather than mandate a "one size fits all" approach.

Submission of scientific information. The FDA 510(k) Working Group recommends that CDRH consider revising 21 C.F.R. "807.87 to explicitly require 510(k) submitters to provide a list and brief description of all scientific information regarding the safety and/or effectiveness of their devices under review. MDMA supports providing material information related to the specific product under review that is fair and balanced. However, requiring submission of "all" scientific information pertaining to a device type is not only overly burdensome and perhaps impossible for the submitter, but would create more work for reviewers who may already be familiar with the device type.

Postmarket requirements. MDMA supports reasonable postmarket requirements when balanced with the premarket process. However, postmarket surveillance should not be required as condition of clearance. CDRH currently has more than adequate postmarket authority, including special controls for class II devices.[12] Furthermore, although implementation of a unique device identification ("UDI") system should allow for better collection of "real-world" data, FDA must maintain this database and prohibit UDI data from being used by third parties to exclude device manufacturers from gaining access to hospitals.

In conclusion, MDMA appreciates the opportunity to provide these initial comments on the preliminary reports and looks forward to providing additional, more detailed comments, once FDA provides more information regarding each of the specific proposals. In the meantime, if MDMA can provide additional assistance, please do not hesitate to contact the undersigned.

Respectfully Submitted,

Mark B. Leahey
President " CEO
Medical Device Manufacturing Association

[12] 21 U.S.C. "360c(a)(1)(B); "522 orders" for postmarket studies.

October 4, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

RE: Docket No. FDA-2010-N-0348: Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations; Availability; Request for Comments

To Whom It May Concern:

The **Society for Women's Health Research (SWHR)** appreciates the opportunity to comment on the importance of device innovation and the opportunities that we face in bringing about lasting changes to the 510k process.

SWHR, a national non-profit organization based in Washington DC, is widely recognized as the thought leader in research on sex differences and is dedicated to improving women's health through advocacy, education, and research. SWHR was founded in 1990 by a group of physicians, medical researchers and health advocates who wanted to bring attention to the myriad of diseases and conditions that affect women uniquely. Women's health, until then, had been defined primarily as reproductive health. Women were not routinely included in most major medical research studies and scientists rarely considered biological sex as a variable in their research. The focus since 1995 has been to clearly demonstrate that sex and gender differences exist, and that more research needs to be done to explore conditions that affect women differently, disproportionately, or exclusively—to identify these differences and to understand the implications for diagnosis and treatment.

In keeping with SWHR's mission, as more sex and gender based differences are found clinically, research and medical practice must stand ready to respond with sex and gender appropriate therapies—medications, procedures, diagnostics, and devices. While we have made great strides in raising the social conscious about sex-based differences in cardiovascular, musculoskeletal, and behavioral health issues (among others) there is still a paucity of medical care options tailored to an individual based on sex—few devices and no FDA approved medications indicated for both sexes differentiate use based on sex, despite now decades of research on biological, cellular, physiological and endocrine based differences. The 510k process has served as a means for quickly advancing minor improvements to women's health care, such as improved gynecological ablation techniques. Over time, these minor advancements can lead to significant improvements in women's health care.

One clear example where research is not serving women's health interests is heart disease. Women suffer different side effects during a heart attack. Women are more likely to die after a heart attack. Research is showing that the actual intrinsic beating style, twisting, and contracting of a woman's heart differs from a man—yet pacemakers can be designed and approved based on a standard patient model, and heart disease

continues to be the number one killer of women. It is within this approval process that the FDA is uniquely situated to ask for sex based analysis of research. Raising expectations for this type of research, even if it only results in minor modifications, may finally start eliminating some of the disparities that persist between women and men in health care today.

Having both a standard and accelerated approval process in place for devices, diagnostics, and medications is a good model so long as each process is standardized and identifies with patient need. Standard and accelerated approvals need to ensure proper safety, surveillance and diligence before, during, and after the approval process. While a review of the percentages of devices undergoing a 510k review is past due, we hope that the FDA will cautiously balance any changes to the approval process with the needs of patients, health care providers, and the companies bringing these new and innovative tools to market. Accelerated approval processes play a key role in advancing improvements in current options (and hopefully more sex-based advancements) for patients in a timely fashion. A FDA approval process that is unpredictable or burdensome may have the unintended side effect of discouraging and stifling innovation in the smaller fields (and often less profitable fields) such as sex-based research. The FDA needs to ensure companies are informed and prepared for whichever approval process is deemed appropriate.

We hope that such considerations will be discussed during the improvements to the 510k process. SWHR supports those researchers and companies working to bring improved care to women and men through personalization of their product. We all need to do our part to encourage sex differences research so that all patients have timely access to care that has been researched and documented in patients like themselves and with the best opportunity to improve health.

Sincerely,

Phyllis Greenberger, MSW
Society for Women's Health Research, President and CEO

62 Columbus Street, Charleston, South Carolina 29403

October 4, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2010-N-0348

Dear Dr. Hamburg:

Thank you for the opportunity to provide feedback on the FDA's recommendations for changes in the 510K device approval process and requirements of manufacturers. As the world's largest and most prolific consumer education and patient advocacy organization in the field of incontinence, we are pleased to see that the FDA has reviewed its process and procedures for approving 510K devices and believe that such a review should routinely take place as part of the agency's dedication to its own, internal continuous quality improvement. As the sophistication of devices increases, in part by the expansion of globally accessible technology, we applaud the acknowledgement of the FDA of the need to elevate the training and development of its reviewers and support staff. Clarifying definitions and refining guidance documents can only improve the quality of submissions and should reduce management time of manufacturers otherwise seeking clarifications and reduce downtime during the review process when questions are asked and additional information is sought by the FDA reviewers. These are all sound recommendations, in our opinion.

As you know, the National Association For Continence (NAFC) is a proponent of change and innovation. Representing the voices of an estimated 25 million adult Americans facing problems of bladder and bowel control, NAFC wants to bring safer, more efficacious, and more cost effective and lasting solutions to patients suffering with this spectrum of pelvic floor disorders, male and female alike. We don't want anything to retard the progress that industry and healthcare providers are already making available. To that end, we are opposed to tying the hands of doctors by prohibiting "off

label" usage of devices, as that is often the very first step in innovation that leads to the next generation of devices or which unearths an application that may be even superior than the originally intended use.

Having said that, we advocate a stronger effort by the FDA on post-market surveillance, on all devices and drugs. The data collection and analysis are missing in too many instances. And randomized clinical trials, by definition, can't possibly generate results that are generalizable to the whole population. While medical societies are sometimes organized to collect and interpret their own data, this is limited by funding that individual doctors receive largely from industry for their time and expenses. Moreover, professional societies do not always do the best job of self-policing or imposing restrictions on how surgery or medicine is to be practiced. I trust that the FDA will make post-market surveillance a priority in its future work.

Thank you for all you do to keep America safe and healthy. And thank you for your consideration of this feedback.

Sincerely,

Nancy Muller
Executive Director

Comments by CONNECT

Submitted to the Food and Drug Administration

Related to the Request for Comments on

The CDRH 510(k) Working Group and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Reports and Recommendations,

Docket No. FDA-2010-N-0348

October 4, 2010

Summary:

CONNECT's mission is to propel innovative ideas and emerging technologies to the marketplace by connecting entrepreneurs with the comprehensive resources they need to sustain viability and business vibrancy. That mission could be hindered in the medical device field if the Food and Drug Administration does not exercise regulatory caution and restraint as it seeks to reform the 510(k) review process. The legal, policy and practical uncertainties that are inevitable if restraint is not exercised could possibly dampen innovation in the field.

On the other hand, if caution is exercised with an eye to the needs of innovation, especially start-up innovation and emerging technologies, the process could be enhanced in a way that further promotes and protects public health. In the absence of a clear and readily identifiable public health threat, CONNECT respectfully requests that the FDA continue to evaluate and analyze potential regulatory changes toward the goal of increased uniformity and act only where consensus exists that innovation will be accelerated and patient care advanced. Where the lack of consensus yields valid but contrasting arguments, the FDA should seek further input and use its ability to convene

University of California—Washington Center
1608 Rhode Island Avenue, NW • Office 245 • Washington • DC • 20036

disparate voices toward an outcome that will clearly advance innovation and patient care.

Introduction:

CONNECT is a nonprofit organization, birthed out of the University of California—San Diego, that is dedicated to creating and sustaining the growth of innovative technology and related businesses. Since 1985, CONNECT has assisted in the formation and development of over 2,000 companies across a broad spectrum of technologies and is widely regarded as one the world's most successful regional programs linking inventors and entrepreneurs with the resources they need for success. The spectrum of technologies fostered includes IT, wireless, software, clean energy, environmental, life sciences/biotech, defense and security, and sports/action technologies. CONNECT focuses on research institution support, business creation and development, entrepreneurial learning, access to capital, protection of intellectual property, public policy advocacy, awards, recognition and networking. More than 40 countries and regions have adopted the CONNECT model, including New York City, the U.K, Sweden, Norway, Denmark, Australia and India.[1]

As a leading voice in the innovation community, especially the voice of the start-up innovator, CONNECT believes it is compelled to add its unique perspective to the voices being heard by the FDA. CONNECT heartily commends the FDA and the CDRH for commissioning the two reports and being transparent in publishing the reports followed by seeking public comment. It is refreshing to see a public agency admit weaknesses in its regulatory processes and then seek input on addressing those weaknesses. CONNECT hopes the officials reviewing these comments will appreciate the cautions expressed herein and will only advance policies that the innovation

[1] To learn more, go to www.CONNECT.org

community agrees will clearly promote device advancements and improved patient care.

I. The Agency should recognize that the current pace of innovation in the medical device field is moving at a rate that eclipses the CDRH's ability to regulate in anticipation of changing innovation trends to improve patient care.

The U.S. and the world stand at the frontier of a true healthcare revolution as technology changes the face of healthcare diagnosis, treatment, and delivery while also changing the interactions of the doctor-patient relationship. As such, the CDRH is certain to see continued change and innovation from the medical device industry. Additionally, technology could create convergences between industries that have not previously been interrelated. For example, the new convergence taking shape in the wireless health sector will undoubtedly create new devices that could lead to significant changes in patient care. Technologies and devices that are common today might be obsolete in as little as 24 months.

Even in optimal political settings, legislative and regulatory bodies simply cannot keep pace and legislate/regulate in anticipation of innovation trends and their market repercussions. Thus, modern day efforts to promulgate broad and sweeping regulatory changes run the risk of being unworkable and inflexible in the face of innovation. Furthermore, such broad and sweeping changes disproportionately impact small innovators and start-up companies in an inequitable way. Start-up companies face numerous hurdles in just keeping their company viable while simultaneously trying to advance the commercialization of their device. If the CDRH promulgates multiple rules that significantly change the face of the approval pathway, the small innovators' lack of resources will put them at a competitive disadvantage against larger players. Accentuating the already difficult market forces start-up companies face will relegate to the valley of death devices that might succeed through current pathways.

II. Because of the rapid pace of innovation and the limits of the legislative and regulatory process, the CDRH should marshal its finite resources toward retaining the current advantages of regulatory certain approval pathways and the flexibility that will enable further innovation and improved healthcare outcomes.

In the vast majority of cases, the current regulatory approval pathways are working in a way that allows innovative change and advances patient care. In the absence of a major and significant public health threat, the CDRH should focus its resources on how to improve the flaws in the current system and not on how to promulgate significant changes that will reshape current understandings and inject more uncertainty into the system.

The reports of the Taskforce and Working Group highlight some of the current gaps in the system where confusion or conflict exists in the way the approval process is implemented by the Agency. Attacking those gaps in a measured, careful and transparent way, will allow innovators, including small start-ups, to have greater certainty in how to develop their creations and bring disruptive innovations to the marketplace. The goal of the agency should be to capitalize on its power of convening and synthesizing the expertise of innovators in such a way to increase uniformity and clarity which will level the competitive playing field for all innovators. Not only will such an approach deliver better health outcomes but it will best utilize the agency's resources which are likely to be limited in the political climate of the foreseeable future.

In the alternative, the agency should not proceed with promulgating broad regulatory changes until it has issued an "Innovation Impact Statement." Similar to the requirements of the Regulatory Flexibility Act as it applies to regulatory impacts on small businesses, the Innovation Impact Statement would explain to the public 1) what impact the regulation will have on innovation, 2) what data and analysis were used to reach the agency's conclusion regarding the regulation's impact on innovation, 3) the particular impact on emerging technologies in the industry or related industries, 4) the cost to start-up businesses in the industry or related industries, and 5) the trends in the public comments related to the regulation's impact on innovation and start-up business.

Conclusion:

Because the legal, policy and practical consequences of broad and sweeping reform are likely to inject uncertainty into the innovation process which will hamper emerging technologies and devices, CONNECT respectfully requests that the Agency focus on increasing uniformity and certainty in the existing 510(k) approval process with the input of innovative voices, including those of the start-up community. In the alternative, the agency should first issue an Innovation Impact Statement which fully

analyzes and explains the impact of broad regulations on America's device innovation landscape.

Respectfully submitted,

CONNECT, by:

Timothy Tardibono

Timothy Tardibono, M.A., J.D.
Public Policy Director
timothy@connect.org
202.412.7791 (cell)
202.974.6366 (office)

October 4, 2010

BY ELECTRONIC DELIVERY

Jeffrey Shuren, M.D., J.D.
Director
Center for Devices and Radiological Health
10903 New Hampshire Avenue
WO66-5429
Silver Spring, MD 20993

Re: Docket No. FDA-2010-N-0348: The "510(k) Working Group Preliminary Report and Recommendations" and the "Task Force on the Utilization of Science in Regulatory Decision Making: Preliminary Report and Recommendations"

Dear Dr. Shuren:

SonoSite, Inc., appreciates the opportunity to provide comments on the recent draft reports with recommendations released by the U.S. Food and Drug Administration (FDA) regarding proposed changes to the 510(k) clearance process. SonoSite is a manufacturer of high quality, portable ultrasound systems located in Bothell, Washington. SonoSite manufactures and markets ultrasound systems that provide complete diagnostic ultrasound studies and are optimized for use at the point of care. SonoSite's products are used in physician offices and other sites of care, such as hospitals and free-standing imaging labs, to provide a wide variety of diagnostic and imaging guidance ultrasound services. SonoSite is also a member of the Medical Imaging and Technology Alliance (MITA) and supports the comments submitted by MITA to the FDA on this same subject.

Below are detailed comments from SonoSite outlining our recommendations on specific areas of the report that are of greatest concern to us with regard to continued support by the FDA of a clearance process that embraces innovation for and evolution of ultrasound technology, a common and vital tool, which has enjoyed widespread use in medical practice for more than 30 years.

We ask FDA to consider the following comments and recommendations:

- SonoSite recommends that FDA use a formal notice and comment process for any guidance, regulations or proposed legislation developed by the FDA where the purpose is

the implementation of policy changes proposed in either of these two reports. We believe strongly that the implementation of policies articulated in the reports must first be preceded by the publication of the details associated with them, and that the public must then be provided sufficient time for public comments to FDA on these more detailed recommendations, prior to implementation, regardless of whether the reform/change is being implemented using a guidance document, a regulation or legislation.

- Regarding the Section 5.1.2.3 (Report, Vol. I, page 62): Multiple Predicates, SonoSite would not support any specifics recommendations in such a guidance that would in any way narrow the use of multiple predicates as a safe and effective means of demonstrating substantial equivalence (SE) to previously cleared devices. As just one of the manufacturers of ultrasound systems, SonoSite has four different product lines of ultrasound systems, each with its own unique set of design features and functionalities. If FDA were to narrow the scope of the use of multiple predicates for the purpose of demonstrating SE, SonoSite's ability to create new ultrasound systems that combine the various functions and features of our current product lines in new form factors to advance the practice of medicine would be hindered.

- Regarding Section 5.2.1.3 (Report, Vol. I, page 76) Class IIb Classification, If the FDA were to move forward with the creation of a Class IIb classification utilizing the sample definition included in the Reports, SonoSite would not support ultrasound systems being included in those devices designated at Class IIb and we do not believe that the definition as currently drafted includes imaging devices. Ultrasound uses acoustic energy at levels that are not great enough to alter atoms and molecules and permanently damage biological tissues. There is no ionizing radiation exposure hazard with this imaging modality. There are no known risks to ultrasound imaging. The inherent safety of ultrasound makes it one of the lowest risk imaging modalities. With the safeguards on the machines used to regulate the acoustic output, even a very minimally trained operator would be very unlikely to cause any patient harm.

- Regarding Section 5.2.1.1 (Report, Vol. I, page 67) Unreported device modifications, SonoSite believes this requirement is unnecessary and duplicative of the review process that occurs during an FDA inspection. All manufacturers currently keep records of changes which they make to their devices on file where the devices are manufactured, in accordance with current FDA guidance on determining when a device modification requires a premarket notification, which are all open to and inspected by the FDA.

- Regarding Section 5.3.1.2 (Report, Vol. I, page 95) Third party review, SonoSite strongly supports the third-party review program and opposes efforts to limit this program. The third-party review program has proven to be an effective, efficient system to get low-risk products (including ultrasound devices) to patients faster and without burdening CDRH staff. SonoSite has successfully used the third party review program in securing FDA clearance of its products. However, processing performance under the program has deteriorated over the last several years, with total review times increasing by as much as 4 times the total review times in the first years of the program. We would ask the FDA to define its process for reviewing third party recommendations in order to avoid complete,

duplicative reviews, and establish and share with the community performance goals regarding acceptable total review times.

Background

Implementation of Report Recommendations Must Include Additional Opportunities for Public Comment

SonoSite is concerned that the FDA's recently issued reports regarding proposed reforms to the 510K process are lacking specifics and as a result many of the details necessary to render a decision regarding what level of controversy a proposal invokes, do not exist. In fact, many of the policies in the reports could be both extremely controversial and harmful to innovation or they could be totally benign, or they could be helpful to innovation. However, we can not make such a determination at this time because the reports lack the specific details of how each recommendation would be implemented.

For this reason, we believe strongly that the implementation of policies articulated in the reports must first be preceded by the publication of the details associated with them, and that the public must then be provided sufficient time for public comment to the FDA on these more detailed recommendations prior to implementation, regardless of whether the reform/change is being implemented using a guidance document, a regulation or legislation.

In addition, SonoSite would encourage the FDA to implement the majority of these reforms using regulations and changes in the law. We believe that it is important that FDA use regulations and legislation versus guidance documents ensuring a process that is truly transparent to all stakeholders, including the public. Publications of regulations are subjected to various process rules under the Administrative Procedures Act, including the use of public comment periods and response to submitted comments. Given the potential impact level of some of the changes that FDA is proposing this level of transparency and stakeholder involvement is essential. We believe it is only when these more stringent regulatory and legislative processes are utilized that broad-based consensus is reached and enduring policies are implemented.

Use of Multiple Predicates, as detailed in Section 5.1.2.3 (Report Vol. I, page 62)

While SonoSite appreciates that FDA is proposing to develop a guidance document explaining the appropriate circumstances for when multiple predicates may be used, we would not support any specifics recommendations in such a guidance that would in any way narrow the use of multiple predicates as a safe and effective means of demonstrating substantial equivalence to previously cleared devices.

Use of predicate devices for comparison purposes is the essence of the 510(k) process and the use of multiple predicates in 510(k) applications is critically important for demonstrating substantial equivalence (SE). This is particularly true for diagnostic imaging devices, including ultrasound systems, which have a long product life and are continually evolving increased functionality and new device features. Given the changing characteristics of diagnostic imaging devices, use of one predicate may not be sufficient for comparative purposes.

For example, as a single manufacturer of ultrasound systems, SonoSite has four different product lines of ultrasound systems, each with its own unique set of design features and functionalities. If FDA were to narrow the scope of the use of multiple predicates for the purpose of demonstrating SE, SonoSite's ability to create new ultrasound systems that combine the various functions and features of our current product lines in new form factors to advance the practice of medicine would be hindered. Not to mention the ability to use the wide variety of options and features on all marketed ultrasound devices in the field to create new, innovative products.

Finally, as ultrasound guidance is developing as a tool to aid in visualizing other medical procedures, there are increasing applications for ultrasound devices to be coupled with other non-ultrasound technologies that introduce the need to combine several predicates (e.g., drug delivery and catheter guidance devices.) Given these variation in features, it is essential that a device manufacturer have the ability to use multiple predicates so that individual features or technological characteristics on a new device can be compared with similar features on predicate devices.

The quality and types of multiple predicate data submitted with the 510(k) application ensure that multiple predicates in themselves do not pose any additional risks when compared to 510(k) applications that only use a single predicate to prove SE. As FDA is aware, the 510(k) submission data is arrived at by testing and analyses on the totality of the new device design. Mandated Design Controls that ensure the safety and effectiveness of the new device are completed and the results provided in the 510(k) submission including verification, validation and risk management performed on the new device which is being compared to multiple predicates.

SonoSite would be happy to participate with FDA in providing additional training to its reviewers on how to address 510(k) applications which use multiple predicates for comparison purposes. SonoSite would be willing to bring its suite of products to the FDA and break them down for staff to learn the various components and how those various components of the product relate to the need to use multiple predicates. Provision of detailed and ongoing training related to multiple predicates will facilitate clarity and minimize confusion during the review process.

Section 5.2.1.3 (Report, Vol. I, page 76): Class IIb Classification

FDA is proposing that CDRH develop guidance defining a subset of class II devices, called "Class IIb" devices, for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting will *typically* be necessary to support a substantial equivalence determination.

If the FDA were to move forward with the creation of a Class IIb classification utilizing the sample definition included in the Reports, SonoSite would not support ultrasound systems being included in those devices designated at Class IIb and we do not believe that the definition as currently drafted includes imaging devices.

Medical ultrasound imaging was developed from sonar and radar technology and has had widespread use for more than 30 years. It is a common and vital tool used by licensed health care professionals and with a physician's prescription for monitoring fetal health and internal organs, and for diagnosing many conditions.

As the FDA knows, ultrasound imaging (sonography) uses high-frequency sound waves to view soft tissue such as muscles and internal organs. Because ultrasound images are captured in real-time, they can show movement of the body's internal organs as well as blood flowing through the vessels.

Ultrasound uses acoustic energy at levels that are not great enough to alter atoms and molecules and permanently damage biological tissues. There is no ionizing radiation exposure hazard with this imaging modality. There are no known risks to ultrasound imaging. The inherent safety of ultrasound makes it one of the lowest risk imaging modalities. With the safeguards on the machines used to regulate the acoustic output, even a very minimally trained operator would be very unlikely to cause any patient harm.

SonoSite recommends that FDA work with industry to identify on a case-by-case basis those devices for which additional requirements could be applicable, versus creating a Class IIb product designation. It is essential for the timely introduction of innovative new devices that there is predictability in FDA's classification process so that manufacturers of any given device type understand how that device is classified when they start the design. One example, FDA could consider in create this case by case process is the GHTF system in Europe.

Section 5.2.1.1 (Report, Vol. I, page 67): Unreported device modifications

FDA is proposing the creation of a requirement where each manufacturer would provide regular, periodic updates to the Center listing any modifications made to its device without the submission of a new 510(k).

SonoSite believes this requirement is unnecessary and duplicative of the review process that occurs during an FDA inspection. All manufacturers currently keep records of changes which they make to their devices on file where the devices are manufactured, which are all open to and inspected by the FDA. This new requirement would only provide FDA with redundant information already provided with the 510(k) submission. Device modifications are undertaken according to Design Control requirements, documented and made available to FDA during inspections. SonoSite believes that the current policy which leaves it to the discretion of the manufacturer to make the determination of when a device modification would warrant filing of a new 510(k) has not jeopardized the public health and thus should be maintained.

Section 5.3.1.2 (Report, Vol. I, page 95): Third-Party Review

FDA is proposing that CDRH develop a process for regularly evaluating the list of device types eligible for third-party review and adding or removing device types as appropriate based on available information. It has also been proposed that CDRH enhance its third-party reviewer training program, and consider options for sharing more information about previous decisions

with third-party reviewers, in order to assure greater consistency between in-house and third-party reviews.

SonoSite strongly supports the third-party review program and opposes efforts to limit this program. The third-party review program has proven to be an effective, efficient system to get low-risk products to patients faster and without burdening CDRH staff. SonoSite has successfully used the third party review program in securing FDA clearance of its products. The third-party review program was a key agreement contained in the MDUFMA legislation, and its purpose was and is to streamline the 510(k) process. The third-party review program worked well during those first years of its existence and it played a key role in reducing the FDA processing time for 510(k) applications. However, processing performance under the program has deteriorated over the last several years, with total review times increasing by as much as 4 times the total review times in the first years of the program. We believe this is due in large part to a lack of consistency between FDA regulatory expectations and third-party reviewers' understanding of those expectations.

SonoSite would ask that the FDA establish clear guidance for when third party review is appropriate, define FDA's process for reviewing third party recommendations in order to avoid complete, duplicative reviews, and establish and share with the community performance goals regarding acceptable total to regarding review times.

FDA should ensure that any changes to the program do not result in a decrease in the number of products eligible for third party review and that FDA not put in place other obstacles to using third party review. SonoSite strongly supports the continued use of the third-party review program to realize the benefits of a more efficient 510(k) process. SonoSite agrees that CDRH should enhance its third-party reviewer training program, as well as share more information about previous FDA decisions with third-party reviewers. This should help improve consistency between third-party reviewers' understanding and FDA regulatory expectations. SonoSite would be happy to work with FDA on review training and other mechanisms to strengthen the third party reviewer program.

Conclusion

In conclusion, SonoSite urges FDA to consider these comments as it moves forward to provide stakeholders with specific details regarding how FDA would implementation any policies changes as outlined in the 510K reports and then additional opportunities for us to provide FDA with comments on said specifics.

SonoSite, Inc. appreciates the opportunity to provide comments on these proposed changes in FDA's policies. If SonoSite can provide FDA with additional information regarding this matter, please do not hesitate to contact me at 425-951-1275 or Mary.Moore@SonoSite.com.

Sincerely,

Mary K. Moore
Vice President, Regulatory Affairs

SonoSite Inc.

MITA
MEDICAL IMAGING
& TECHNOLOGY ALLIANCE
A DIVISION OF NEMA

1300 North 17th Street ▪ Suite 1752
Arlington, Virginia 22209
Tel: 703.841.3200
Fax: 703.841.3392
www.medicalimaging.org

October 4, 2010

Jeffrey Shuren, M.D., J.D.
Director
Center for Devices and Radiological Health
10903 New Hampshire Avenue
WO66-5429
Silver Spring, MD 20993

Re: The "510(k) Working Group Preliminary Report and Recommendations" and the "Task Force on the Utilization of Science in Regulatory Decision Making: Preliminary Report and Recommendations"

Dear Dr. Shuren:

The Medical Imaging and Technology Alliance (MITA) appreciates this opportunity to comment on the recent draft reports, (the Reports) with recommendations released by the U.S. Food and Drug Administration (FDA) regarding proposed changes to the 510(k) clearance process. As the leading trade association representing medical imaging and radiotherapy technology manufacturers, we have an in-depth understanding of the significant benefits to health that medical imaging, radiotherapy and proton therapy provide.

Medical imaging encompasses X-ray imaging, computed tomography (CT) scans, radiation therapy, related image acquisitions, diagnostic ultrasound, nuclear medical imaging (including positron emission tomography (PET)), magnetic resonance imaging (MRI) and imaging information systems. Medical imaging is used to diagnose patients with disease, often reducing the need for costly medical services and invasive surgical procedures.[1] In addition, medical imaging equipment often is used to select, guide and facilitate effective treatment, for example, by using image guidance for surgical or radiotherapeutic interventions.[2] MITA's members also develop and manufacture innovative radiotherapy equipment used in cancer treatment.

MITA looks forward to working with you to continue to improve the healthcare of all Americans through a clearance process that promotes innovation, enhances regulatory predictability,

[1] See, e.g., Multidetector-Row Computed Tomography in Suspected Pulmonary Embolism," Perrier, et. al., New England Journal of Medicine, Vol 352, No 17; pp1760-1768, April 28, 2005.
[2] See, e.g., Jelinek, JS et al. "Diagnosis of Primary Bone Tumors with Image-Guided Percutaneous Biopsy: Experience with 110 Tumors." *Radiology*. 223 (2002): 731 - 737.

improves patient safety and protects the public health. Without a robust and innovative imaging and radiation therapy industry, the early detection, diagnosis, staging, therapy, and surveillance of many diseases will be compromised.

General Comment on Process and Scope

Overall, the Reports recently issued by the Agency are extremely broad in their scope. As a result, many of the necessary details of the policies articulated in the documents remain to be determined. In fact, many of the policies in the Report could be either controversial and damaging to innovation or benign, based entirely on the details. For these reasons, we believe strongly that the implementation of policies articulated in the Reports must be preceded by the publication of the details associated with them, and that the public must be provided sufficient time to provide public comment on those more detailed proposals.

In addition, the Reports appear to have taken a generally expansive view of FDA authorities and tend to prefer the use of guidance over regulation, and regulation over changes in law. MITA companies believe it is essential that on issues that have the potential to be extremely controversial, and which have such an enormous impact on innovation and the public health, it is important for the Agency to instead opt for more stringent and public processes in order to ensure that the legal rights of stakeholders are protected, the opportunity to provide public comment is ensured and the legislative process is engaged. To that end, MITA believes it is critical that FDA publish detailed draft proposals, and allow for public comment followed by final regulations. It is only when these more formal and public regulatory and legislative processes are utilized that broad based consensus is reached and enduring policies are implemented.

MITA also recommends that the FDA prioritize their efforts by focusing on a select few high-priority proposals. By prioritizing among the proposals, stakeholders can then provide high quality, focused and detailed responses on the most likely agency actions. Such a process would conserve agency resources, reduce the burden on stakeholders, improve the quality and specificity of proposals and responses, and speed the completion of the 510(k) reform effort.

In setting the Agency s priorities, FDA should consider the direct and societal cost of their proposals, including cost and burden on the Agency, manufacturers, patients and providers. We also urge the FDA to consider the impact of delays in clearance, scuttled product development, reduced innovation, and lost jobs. Unwise changes have the very real possibility of increased cost of products, delayed/denied access to products, lost jobs, export of R D, negative impact on the economy and adverse impact on the trade balance.

We are very concerned that if the Agency should attempt to implement the broad scope of changes included in the Reports that it would bring the Agency s current activities to a halt and move the Agency away from an appropriate focus on clearing products for market.

As mentioned earlier, the Reports cover an enormous scope. As a result, this letter focuses on those issues of greatest concern to MITA member companies. It is important to note that not commenting on a provision does not imply MITA support for the provision. In fact, virtually all

of the provisions in the Report could be controversial and cause concern to the device industry based on the details not yet provided or could be constructive as details are worked out. We have focused our comments on those issues that cause the greatest concern. Numeric references refer to numbered sections in Volume I or Volume II of the Reports, specifically "CDRH Preliminary Internal Evaluations – Volume I, 510(k) Working Group Preliminary Report and Recommendations, August 2010," and "CDRH Preliminary Internal Evaluations - Volume II, Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations, August 2010," cited herein as Volume I or Volume II.

I. MITA Comments on Recommendations Related to Predicate Devices

Section 5.1.2.3: Use of "Split Predicates" and "Multiple Predicates"

Section 5.1.2.3 (Report, Vol. I, page 62): Multiple Predicates

FDA Proposal: FDA has proposed the development of a guidance document on the appropriate use of more than one predicate, explaining when multiple predicates may be used.

MITA Response: MITA supports the use of multiple predicates as a safe and effective means to demonstrate substantial equivalence to previously cleared devices. Use of predicate devices for comparison purposes is the essence of the 510(k) process. Further, the use of multiple predicates in 510(k) applications is critically important for demonstrating substantial equivalence (SE) to predicate devices in 510(k) applications.

The quality and types of multiple predicate data submitted with the 510(k) application ensure that multiple predicates in themselves do not pose any additional risks when compared to 510(k) applications that only use a single predicate to prove SE. The 510(k) submission data is arrived at by testing and analyses on the totality of the new device design. Design controls that ensure the safety and effectiveness of the new device are completed and the results provided in the 510(k) submission including verification, validation, and risk management performed on the new device that is being compared to multiple predicates.

Prior to restricting the use of multiple predicates, it is incumbent upon the Agency to provide evidence demonstrating an increased risk associated with these products. At the moment, it is not clear why FDA believes risks are introduced with use of multiple predicates and industry would like further clarification.

Examples where multiple predicates have been used in the clearance of diagnostic imaging devices include:

- *X-ray wireless imaging:* Two predicates were used to demonstrate SE. A cleared predicate was used to demonstrate SE to the X-ray technology and a second cleared predicate was used to demonstrate SE to the wireless technology.

- *Dual CT and Nuclear Medicine Systems:* Two predicates were used to demonstrate SE. A cleared predicate was used to demonstrate SE to the technology of the SPECT system. A second cleared predicate was used to demonstrate SE to the CT system.

- *Ultrasound Biopsy Real-Time Registration Software:* In this case, three predicates were used to demonstrate SE. A cleared predicate was used to demonstrate SE to the Ultrasound technology and indications for use, a second cleared predicate was used to demonstrate SE to the image registration software, and a third cleared predicate was used to demonstrate functionality.

Diagnostic imaging devices have a long product life and are continually evolving in terms of increased functionality and new device features. Given the evolving functionality and features of diagnostic imaging devices, use of one predicate is often insufficient for comparative purposes. Also, there are a very wide variety of options or features on marketed devices in the field. Given this variation in features, it is essential that a device manufacturer have the ability to use multiple predicates so that individual features or technological characteristics on a new device can be compared with similar features on predicate devices. If the Agency were to narrow the scope of multiple predicates it would hinder innovation.

Finally, MITA believes that the FDA should provide additional training to its reviewers on how to address 510(k) applications which use multiple predicates for comparison purposes. Provision of detailed and ongoing training related to multiple predicates will facilitate clarity in application and minimize confusion or inconsistent application of evaluation parameters.

Section 5.1.2.3 (Report, Vol. I, page 62): Split Predicates

FDA Proposal: FDA has proposed that CDRH should explore the possibility of explicitly disallowing the use of split predicates.

MITA Response: MITA supports the use of split predicates as a safe and effective means to demonstrate SE to previously cleared devices. Combining already proven technologies permits better patient care and more efficient delivery of health care. Disallowance of the use of split predicates would stifle innovation, and prevent manufacturers from providing the benefits of new technology to patients. As is the case with multiple predicates, the existence of a wide range of individual features and technological characteristics on existing devices demonstrates the need for manufacturers bringing a new device to market to find appropriate predicate devices to which the new device may be compared.

As with multiple predicates, it is not clear why FDA believes risks are introduced with use of multiple predicates and industry would like further clarification. Prior to restricting the use of split predicates it is incumbent on the Agency to provide evidence demonstrating an increased risk associated with these products.

Like multiple predicates, the 510(k) submission data using split predicates are generated by testing and analyses on the totality of the new device design. Design Controls that ensure the safety and effectiveness of the new device are completed and the results provided in the 510k

submission including verification, validation and risk management performed on the new device which is being compared to split predicates.

An example where split predicates have been used in the clearance of diagnostic imaging devices includes:

- *MR Cardiac Coil:* Two predicates were used to demonstrate SE. A cleared predicate was used to demonstrate SE to the cardiac coil technology and a second cleared predicate was used to demonstrate SE to the cardiac coil indications for use.

CDRH should provide guidance for internal staff and industry on the appropriate use of more than one predicate and split predicate use. Such guidance would provide a foundation to minimize confusion in the application of approval parameters and expectations of information necessary for successful submissions.

Section 5.1.2.3 (Report, Vol. I, page 57): When should a device no longer be a predicate

FDA Proposal: FDA has proposed that it develop a guidance on when a device should no longer be available for use as a predicate because of safety and/or effectiveness concerns.

MITA Response: MITA believes that all cleared and legally marketed pre-amendment devices that have not been rescinded by FDA for safety reasons should be allowed as predicates.

II. MITA Comments on 510(k) Submission Content

Section 5.1.1.1 (Report, Vol. I, page 42 et seq.): Define Key Terms (i.e. intended use)

FDA Proposal: FDA has proposed that it review existing guidance to consolidate the concepts of "*indication for use*" and "*intended use*" into a single term, i.e. "*intended use,*" to reduce inconsistencies in their interpretation and application.

MITA Response: MITA does not support the consolidation of these terms and is very concerned that combining these terms could unnecessarily prevent some products from utilizing the 510(k) process. We also believe that consolidation of "*indication for use*" and "*intended use,*" will confuse, rather than clarify, the regulatory process.

These terms have different meanings and should not be combined into one term. The "*intended use*" of a system describes the general use for which a system was developed. The "*indications for use*" of a system refer to the more specific clinical applications of a device.

Examples of different use of these terms are provided in the following table:

Product	*Intended Use*	*Indications for Use*
MR Coil	The Coil is a receive-only RF coil designed for use with 1.5T MRI systems.	The Coil indications for use included imaging of the heart, mediastinum, and pelvis regions for 2D and 3D Magnetic Resonance Imaging. The nucleus excited is hydrogen.
CT	The system is intended to be used for head and whole body computed tomography.	The system is indicated for head, whole body, cardiac and vascular X-ray Computed Tomography applications in patients of all ages. The device output is a valuable medical tool for the diagnosis of disease, trauma, or abnormality and for planning, guiding, and monitoring therapy.
3D Workstation	To reconstruct 3D images from 2D datasets for viewing by the physician.	Indications for use include: orthopedic templating, virtual colonoscopy, intra-cerebral navigation for brain surgery, and tumor localization for radiation treatment planning.

A device for which 510(k) clearance is sought may have the same *"intended use"* as the selected predicate, but may differ in its *"indications for use" (*see example above). FDA acknowledges in the Report that CDRH has not consistently set forth the distinction between *"indications for use"* and *"intended use"* with respect to making a substantial equivalence determination (See Report, page 43).

These inconsistencies create needless confusion in the 510(k) process. A requirement to consolidate *"indications for use,"* with *"intended use"* would stifle innovation and unduly restrict manufacturers in bringing new technology to market, since applicants would be unable to claim substantial equivalence for a new device to a predicate if the new device had different *"indications for use"* even if the new device had the same *"intended use"* as the predicate. MITA recommends that in lieu of consolidation, FDA clarify existing guidance as to the meaning and use of these terms and provide examples that illustrate the difference.

Section 5.1.1.1 (Report, Vol. I, page 49 et seq.): Off–label use

FDA Proposal: FDA has proposed that CDRH explore the possibility of pursuing a statutory amendment to section 513(i)(1)(E) of the Federal Food, Drug and Cosmetic Act that would provide the Agency with express authority to consider an off-label use, in certain limited circumstances, when determining the *"intended use"* of a device under review through the 510(k) process.

MITA Response: MITA does not support this statutory change and believes that this proposal could be implemented in a manner requiring manufacturers to provide possible off-label use to the Agency. Clearly, how physicians use imaging devices is a question for the practice of medicine which is neither in the purview of the device manufacturer or the Agency. In fact, the law clearly states that the Agency is required to review the intended use of a device as it is, not how it might be (see 21 U.S.C. 360(c) (i) (E)) (i)).

In addition, we are concerned that this would have linkage to the potential revised definition of *"intended use,"* and would create further confusion.

Section 5.2.2.2: (Report, Vol. I, page 86): Submission of Labeling Changes

FDA Proposal: FDA has proposed that manufacturers submit all changes to labeling for preclearance.

MITA Response: MITA does not support labeling submission and review for minor labeling changes. However, in instances of significant changes to the product requiring a 510(k) submission, MITA could support a labeling submission requirement as part of the application process provided it is not a condition of clearance or that review of the label delays the clearance process.

Section 5.2.1.2 (Report, Vol. I, page 71): Assurance Cases

FDA Proposal: FDA has proposed that CDRH should consider adopting the use of an "assurance case" framework for 510(k) submissions.

MITA Response: MITA believes that the assurance case framework should not be routinely applied to all 510(k) applications. The adoption of an "assurance case" framework as described would create a significant increase in the regulatory burdens to manufacturers, by requiring substantial, additional documentation to be submitted in the 510(k) process.

The "assurance case" framework was intended to be applied to devices which have been subject to numerous recalls and product failures. Therefore, this highly burdensome process should not be routinely applied to all 510(k) applications. To universally apply a highly detailed "assurance case" framework to all 510(k) applications would be inappropriate and would impede the flow of the 510(k) process for low to moderate risk devices such as medical imaging devices. MITA believes that if the Agency is considering adoption of an "assurance case" framework for 510(k) applications, the level of detail required to be provided in the "assurance case" should be based on the risk level and relative novelty of the device. Further detail on the scope and documentation which would be required under an "assurance case" framework is needed from FDA.

Section 5.2.1.3 (Report, Vol. I, page 76): Class IIb Classification

FDA Proposal: FDA has proposed that CDRH develop guidance defining a subset of class II devices, called "Class IIb" devices, for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting, will *typically* be necessary to support a substantial equivalence determination.

MITA Response: In our view, FDA lacks the statutory authority to create a new class. FDA may not circumvent this required authority by framing Class IIb as something less than a new class.

MITA does not support the creation of a Class IIb classification utilizing the sample definition included in the Reports. While MITA believes that the definition as currently drafted excludes imaging and radiation therapy devices, we still do not believe that the version as drafted is

supported by broad evidence of a safety problem. Instead, the Agency should consider additional requirements on a case-by-case basis.

Just as important, the FDA has not demonstrated that there is a group of 510(k) products that, as a class, require some additional requirements. If a new class is warranted, FDA should set forth the data supporting the need for such a new classification and engage industry and Congress before requesting public input on a specific proposal.

MITA understands that the Agency may, on a case-by-case basis, have reason to demand specific, additional requirements for select products. But class-wide special controls, as described by CDRH, are not an appropriate use of those mechanisms. FDA should consider any new requirement only after product-by-product consideration, as required by the statute, and as the most effective way to match requirements to products and therefore to effectively improve patient safety. Broad, automatic requirements based on classification rather than specific risk profiles and product characteristics would not effectively benefit patients, would disrupt innovation, and would delay patient access to products.

MITA recommends that industry work with FDA to identify on a case-by-case basis those devices for which additional requirements could be applicable. It is essential for the timely introduction of innovative new devices that there is predictability in FDA's classification process so that manufacturers of any given device type understand how that device is classified when they start the design.

In terms of manufacturing information, or potentially additional postmarket evaluation, MITA recommends that this apply only on a case-by-case basis devices that are clearly defined and developed jointly with industry. MITA recommends that industry work jointly with FDA to identify those devices for which additional requirements would be applicable, what type of clinical evaluation data, manufacturing data or postmarket evaluation would be most appropriate based on specific risks identified, rather than applying these requirements across the board.

Section 5.2.1.3 (Report, Vol. I, page 80): Pre-clearance inspections

FDA Proposal: FDA has proposed that CDRH should clarify when it is appropriate to use its authority to withhold clearance on the basis of a failure to comply with good manufacturing practices in situations where there is a substantial likelihood that such failure will potentially present a serious risk to human health, and include a discussion of pre-clearance inspections as part of its "Class IIb" guidance.

MITA Response: MITA does not support a pre-clearance inspection regime as a condition for clearance. The Agency currently has authority to and does presently conduct inspections of manufacturing facilities. Pre-clearance inspections should not be conducted on a routine basis, but should be determined on a case-by-case basis, prioritized and limited to high risk devices.

Section 5.2.1.3 (Report, Vol. I, page 79): Postmarket surveillance studies as condition for clearance of certain devices

FDA Proposal: FDA has proposed greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices.

MITA Response: MITA opposes the use of postmarket surveillance studies as a condition for market clearance.

III. MITA Comments on the FDA 510(k) Process

Section 5.1.3 (Vol. I, Report, page 66): De Novo Process

FDA Proposal: FDA has proposed that CDRH revise existing guidance documents to streamline the current implementation of the De Novo classification process and clarify its evidentiary expectations for De Novo requests.

MITA Response: MITA agrees and believes that the current De Novo process is cumbersome and time consuming. In turn, MITA supports a more effective, efficient, timely and predictable process. In current practice, in those instances in which an appropriate predicate device is unavailable, an applicant cannot initiate the De Novo process until it receives a "Not Substantially Equivalent" (NSE) determination from FDA. Frequently, this is a slow process, which is wasteful of both FDA and industry time and resources.

To improve the de novo process, MITA recommends FDA consider:

1) Eliminating the need to go through the 510(k) (NSE) process prior to commencing the de novo process;

2) Ensuring that classification decisions are based on legitimate risk assessments and the need to ensure patient access to new products;

3) Creating defined time periods for key process steps;

4) Creating a fast track de novo process for obvious Class II products; and

5) Eliminating the need to create new regulations or special controls unless needed on a case by case basis.

MITA believes that FDA should give consideration to the following options under the De Novo Process: However, we ask FDA to note that, currently, the two categories of devices described below would not be eligible for FDA's existing 510(k) process because either a predicate does not exist, or because the predicate is not considered completely adequate.

Generic Devices

For generic devices, consideration should be given to developing a 510(k) clearance process and guidance for devices of a "generic" device type (i.e., devices already regulated under the 510(k) process and having a predicate), which can be considered not substantially equivalent because of minor differences when compared to the predicate for intended use, technological characteristics or performance without predicates. These devices present a low to moderate risk. Conditions for eligibility would include:

- New/modified devices that are of a given generic device type;
- Low to moderate risk devices for which general or special controls or consensus standards are sufficient to provide reasonable assurance of safety and effectiveness; and
- Submission via the 510(k) process. FDA may require data to be submitted which would provide a reasonable assurance of safety and effectiveness.

Non-Generic Devices

For non-generic devices, consideration should be given to developing an improved De Novo process as described above and guidance for devices of low to moderate risk not having a predicate. Using a risk-based approach, FDA may require data necessary to provide reasonable assurance of safety and effectiveness. Conditions for eligibility would include:

- Low to moderate risk devices for which general or special controls or consensus standards are sufficient to provide reasonable assurance of safety and effectiveness; and
- Under the present program, these devices would have been determined to be not substantially equivalent because of differences in intended use, technological characteristics or performance.

MITA recommends that FDA and industry work together to jointly develop a least burdensome De Novo process that would eliminate the current need to go through the traditional 510(k) process steps, only to be found NSE. Furthermore, MITA supports a De Novo process that would allow these devices to be placed on the market prior to the traditional method of developing a Special Control Guidance document which is very time consuming under FDA's current system.

Section 5.1.2.2 (Report, Vol. I, page 58): Rescission Authority

FDA Proposal: FDA has proposed that CDRH should consider issuing a regulation to define the scope, grounds and appropriate procedures for exercise of its authority to fully or partially rescind a 510(k) clearance.

MITA Response: MITA does not support the expansion of the FDA's rescission authority except in the case of a fraudulent application.

In addition, an important question which must be resolved is whether the rescission of a 510(k) clearance would imply that any devices which used the rescinded device as a predicate would

also be rescinded, and how far that logic would be carried, since there could be a string of device/predicates linked to the rescinded device. Rescission of the market clearances of linked devices would be very disruptive to the users of these products and would jeopardize patient care.

Section 5.2.1.1 (Report, Vol. I, page 67): Unreported device modifications

FDA Proposal: FDA has proposed the possibility of requiring each manufacturer to provide regular, periodic updates to the Center listing any modifications made to its device without the submission of a new 510(k).

MITA Response: MITA believes that this requirement is unnecessary since manufacturers are currently required to provide, with each new 510(k) submission, the device modifications made since the last 510(k) filing. Given the number of modifications which are made, this additional requirement would impose significant burdens on industry and provides FDA with redundant information already provided in the 510(k) submission. Device modifications are undertaken according to Design Control requirements, documented and made available to FDA suring inspections. MITA believes that current policy has not jeopardized the public health and thus should be maintained.

IV. MITA Comments on Internal FDA Policies and Procedures

Section 4.3.1(Report, Vol. II, page 35): "Notice to Industry" Letters

FDA Proposal: FDA has proposed that CDRH establish as a standard practice sending open "Notice to Industry" letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations on the basis of new scientific information.

MITA Response: MITA supports additional transparency including the prompt notification of industry by FDA of any new regulatory expectations in order to notify an applicant of changes in that may impact the clearance process.

However, MITA members oppose the use and expansion of Level 1 Guidance to immediately implement new FDA policies. Instead the Agency should work with industry, including two-way dialogue regarding any changes in regulatory expectations.

Section 5.2.2.2 (Report, Vol. I, page 85): 510(k) Database

FDA Proposal: FDA has proposed the development of a database that includes, for each cleared device, a verified 510(k) summary, photographs and schematics of the device. Further the Agency has proposed that the submitter keep at least one unit of a device under review available for Agency access as part of the review or during future reviews in which the device in question is cited as a predicate.

MITA Response: MITA does not support the inclusion of schematics in this proposal as it would lead to the disclosure of proprietary information. Disclosure of such information would be anti-competitive in nature and in opposition to FDA's role in fostering innovation.

In addition, MITA strongly opposes a requirement to keep an inventory of imaging products for Agency review during the application process and into the future to allow for review should the product be used as a predicate. This requirement would place an enormous burden on manufacturers of capital equipment while providing the Agency little benefit. For example, CT and MR machines are extremely large and must be stored in stable environments. The proposed policy recommendation seems to imply the manufacturer would be responsible for keeping each new model in inventory virtually indefinitely.

Section 5.3.1.2 (Report, Vol. I, page 95): Third-Party Review

FDA Proposal: FDA has proposed that CDRH develop a process for regularly evaluating the list of device types eligible for third-party review and adding or removing device types as appropriate based on available information. It has also been proposed that CDRH enhance its third-party reviewer training program, and consider options for sharing more information about previous decisions with third-party reviewers, in order to assure greater consistency between in-house and third-party reviews.

MITA Response: MITA strongly supports the third-party review program and opposes efforts to limit this program. The third-party review program has proven to be an effective, efficient system to get low-risk products to patients faster and without burdening CDRH. The third-party review program was a key agreement contained in the MDUFMA legislation, and its purpose was and is to streamline the flow of the 510(k) process. The third-party review program worked well for the first years of its existence and played a key role in reducing the FDA processing time for 510(k) applications. Processing performance under the program has deteriorated over the last several years due in large part to a lack of consistency between FDA regulatory expectations and third-party reviewers' understanding of those expectations.

MITA urges FDA to establish clear guidance for when and how third party review is appropriate, to define the process for reviewing third party recommendations in order to avoid duplicative reviews, and to establish performance goals to promote better visibility FDA's performance and review times.

MITA believes that rigid rules that limit eligibility of certain types of devices for the program should not be imposed. MITA strongly supports the continued use of the third-party review program to realize the benefits of a more efficient 510(k) process. MITA agrees that CDRH should enhance its third-party reviewer training program, as well as share more information about previous FDA decisions with third-party reviewers. This should help improve consistency between third-party reviewers' understanding and FDA regulatory expectations. MITA recommends that FDA and industry should collaboratively work on mechanisms to strengthen the program.

Lastly, FDA should ensure that any changes to the program do not result in a decrease in the number of products eligible for third party review and that FDA not put in place other obstacles to using third party review.

V. Additional Areas for Comment

Section 5.2.1.2 (Report, Vol. I, page 73): Incomplete information

FDA Proposal: FDA has proposed that CDRH consider revising 21 CFR 807.8 to explicitly require 510(k) submitters to provide a list and brief description of all scientific information regarding the safety/effectiveness of a new device known to, or should be reasonably known to, the submitter.

MITA Response: MITA believes that the current proposal is open-ended and as a result would be unduly burdensome. It is unclear how compliance with this rule would be determined, what would constitute "should be reasonably known to," and, whether FDA would impose penalties against the submitter if there is a disagreement between the submitter and FDA regarding provision of this information. As drafted, MITA opposes this proposal. FDA should provide further clarification of the intent and scope of this proposal.

Section 5.2.1.3 (Report,Vol. I, page 79): Manufacturer Processing Information

FDA Proposal: FDA has proposed that CDRH develop guidance to provide greater clarity regarding what situations may warrant the submission of manufacturing process information as part of a 510(k), and include a discussion of such information as part of its "Class IIb" guidance.

MITA Response: MITA believes that this provision should be applicable primarily for products of higher risk, and is not intended to apply to medical imaging devices, which are not defined as either "life sustaining" or "life supporting." MITA believes that this provision has the potential to impose greater regulatory burdens on manufacturers, without producing a corresponding benefit. Additionally, MITA is concerned that provision of manufacturer process information would result in inappropriate disclosure of proprietary information. MITA believes that FDA should provide additional details to clarify the scope and intent of this proposal.

Section 4.1.3 (Report, Vol. II, page 33): CDRH Science Council

FDA Proposal: The FDA has proposed establishing a CDRH Science Council comprised of experienced employees and managers, including clinical experts to be responsible providing center-side oversight in a range of scientific areas. The Science Council would meet regularly to discuss and assess how to respond to encounters with new science for a particular device type.

MITA Response: MITA supports the development and implementation of a business process for a Science Council to provide a more robust framework for decision-making and predictability. However, it is unclear how the Science Council will operate, who will be eligible to participate as a Council member, and the criteria used to select participants. MITA believes that the FDA should provide additional details to clarify the proposal. In addition, we would not support the

development of a Science Council with the authority to overturn reviewer decisions to clear products for marketing.

MITA supports the risk-based approach for "signal" detection, escalation, deliberation and action. Once the business process and metrics are more established, MITA suggests that CDRH should present the proposal to the public for comment before any implementation. MITA's concern is how detection of new science will be prioritized and what actions may be taken in response to new science.

VI. Conclusion

MITA appreciates this opportunity to comment on the draft study and recommendations that the FDA has put forward regarding the 510(k) clearance process.

Generally, MITA strongly supports the 510(k) process and policies that will make it more predictable and stable for manufacturers while also promoting innovation and protecting the public health. In that effort, FDA must ensure that the 510(k) reform process itself is prioritized and proceeds in a deliberative, thoughtful manner.

As the 510(k) reform process moves forward, the agency should provide adequate time for input and additional notice and comment opportunities for each specific proposal. In addition, MITA would recommend that CDRH consider engaging directly with stakeholders through in-person meetings to discuss reform proposals.

We would also emphasize that to ensure a broadly supported, successful reform process, CDRH should opt for more stringent processes to provide stakeholders with ample opportunity to participate in the process. We urge the FDA to explicitly consider, debate and balance FDA's twin purposes of protecting patients and fostering innovation at every turn.

We would be pleased to answer any questions you might have about these comments. Please contact me at (703) 841-3279 if MITA can be of any assistance.

Respectfully submitted,

Dave Fisher
Executive Director, MITA
Vice President, NEMA

October 4, 2010

Food and Drug Administration
5630 Fishers Lane,
Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2010-N-0348: Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations; Availability; Request for Comments

To Whom It May Concern:

The undersigned organizations appreciate the opportunity to comment on the 510(k) Working Group's Preliminary Report and Recommendations.

As groups representing patients and health care providers we have a deep and long-standing interest in encouraging the development of new treatments and cures and in assuring that medical products are safe and effective. We applaud FDA for its efforts to conduct an in-depth examination of the 510(k) process and for the extensive work and data collection that went into the preliminary report. We are pleased to support several of the FDA recommendations, which we believe will result in a more predictable and consistent process that will help support product innovation and will provide greater assurance to the safety and effectiveness of cleared devices. At the same time, however, we are concerned that many of the recommendations in the report, if implemented, will result in a more burdensome and time-consuming approval process that will discourage development of new treatments, delay availability of improved products to patients and providers and interfere with physician and other health care providers' clinical decision making.

The recommendations of the report must be considered against a backdrop of several key facts. For most products, the 510(k) process has an exemplary record of assuring safety. Studies by the Battelle Memorial Institute, Professor Ralph Hall of the University of Minnesota and Dr. William Maisel of the Medical Device Safety Institute at the Beth Israel Deaconess Hospital in Boston, all show an extremely low recall rate of marketed products, and only a fraction of recalls are due to problems that might conceivably have been identified in the review process.

Recent FDA data shows disturbing trends in the 510(k) process, which result in delays and frustration for manufacturers, providers, and patients alike. Treatment of submissions is less predictable and consistent and both total review time and the time manufacturers spend answering FDA questions about submitted applications have increased substantially. The number of submissions withdrawn has grown significantly, suggesting that FDA requirements have become less clear or new requirements have been arbitrarily applied. Most disturbing, from the point of view of our member organizations, is that manufacturers are more frequently introducing innovative new products in Europe first, delaying access by American patients to treatments and cures by months or even years.

Key recommendations we believe will improve the 510(k) process include proposals included in the "continuous quality assurance section of the report." We believe enhancing the training, professional development, and knowledge-sharing among reviewers and managers, as proposed in this section of the report, is critical to addressing the problems described above as well as assuring the products cleared through the process are safe and effective. We believe the theme expressed throughout the report that FDA should develop more guidance documents would be a significant step forward. Good guidance documents are very

important to ensure consistency of reviews. We also believe the FDA proposal to simplify and improve the "de novo" process for products that are too novel to meet the normal 510(k) "substantial equivalence" test but not risky enough to merit review through the PMA process would be very constructive.

We are also supportive of the general concept of applying special requirements to a small subset of devices. While some the specific requirements discussed in the report may be overly burdensome, the concept of applying special, clearly defined requirements to a small number of types of devices where enhanced premarket and postmarket requirements are appropriate to demonstrate safety and effectiveness is a good one that would both improve FDA's ability to protect the public and provide manufacturers with clear requirements that would need to be fulfilled to get a product of this type cleared. Effective implementation of this recommendation would obviate any need for many of the sweeping changes FDA has proposed to the process, since for the vast majority of device types, the current system is fully effective to assess safety and effectiveness.

While the recommendations above are constructive, we are very concerned about the bulk of the recommendations contained in the section entitled "A Rational, Well-Defined and Consistently Interpreted Review Standard." We believe that redefinition of the term "substantial equivalence" and potential new limitations on acceptable predicates, as well as eliminating the separate classification of intended use and indications for use go to the heart of the current program and have the potential to make approval more time-consuming and to reduce innovation. We are concerned that the proposal to give FDA new authority to consider an off-label use when determining the "intended use" of a device under 510(k) review could negatively impact patient care. Withholding clearance of a technology because the agency believes it may be used for an off-label purpose not sought by the sponsor could prevent technologies from reaching patients in need.

We are concerned that, taken as a whole, the recommendations in the report, if fully implemented, would represent a huge diversion of FDA resources without commensurate gain as well as possibly push technologies that appropriately go through the 510(k) process to go through the Premarket Approval (PMA) process, unnecessarily driving up research costs and delays in patient access.

The process of retraining staff and implementing new procedures and definitions throughout the program poses a real danger of dramatically slowing FDA's approval process and discouraging innovation over an extended transition period. We urge that changes be phased in and that they be limited to those where there is a clear and demonstrated need that requires corrective action.

In assessing every change included in the report, it is vital that the interests of patients and providers in prompt access to new treatments and cures be a key consideration. Changes that may jeopardize that goal should not be made unless there is clear evidence that the changes are necessary to address a demonstrated public health problem.

Thank you for considering these comments.

Sincerely,

The AIDS Institute
American Association of People with Disabilities
America's Blood Centers
Men's Health Network
National Spinal Cord Injury Association
Parkinson's Action Network
The Simon Foundation for Continence
United Spinal Association

1550 Utica Avenue South, #725
St. Louis Park, MN 55416

952.542.3077 PHONE
952.542.3088 FAX

www.lifesciencealley.org

LifeScience Alley™

October 4, 2010

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

http://www.regulations.gov

RE: LifeScience Alley comments regarding the Center for Devices and Radiological Health '510(k) Working Group Preliminary Report and Recommendations', and 'Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations'

Docket No. FDA-2010-N-0348

LifeScience Alley is Minnesota's association for the medical technology industry. Representing 640 companies and 250,000 Minnesotans, LifeScience Alley is the largest state medical technology association in the country. LifeScience Alley (LSA) acts as the industry's central resource for fostering innovation, offering education & networking, creating consensus, and providing a strong, unified legislative voice. Through our combined efforts we seek to advance medical technology for the benefit of patients everywhere.

LSA recognizes the key role played by CDRH in protecting public health and advancing innovation. The study by CDRH of the 510(k) system provides valuable information and insights into the strengths and weaknesses of the 510(k) process. CDRH is to be commended for the open and detailed assessment of the 510(k) process. LSA supports many of the concepts and themes set forth by CDRH including the importance of training, the need to improve the de novo process, and notification of transfers of 510(k) ownership. LSA endeavors to be a value added partner in all efforts to improve the 510(k) system. LSA appreciates the opportunity to comment on the proposed changes to the 510(k) system.

The '510(k) Working Group Preliminary Report and Recommendations' and the 'Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations' contain preliminary discussion topics and not specific proposals. LSA appreciates the opportunity to participate in providing comment and feedback, yet LSA fails to see how detailed comments on the general list of discussion topics presented by FDA can lead to a genuine and productive public comment on the issues. Below, LSA has chosen to comment on some of the more substantive issues due to their serious potential implications to policy and process. After FDA has actual proposals for each of these topics, LSA looks forward to an interactive and cooperative process through which the 510(k) process will be discussed and possible improvements vetted.

1. **LifeScience Alley is not aware of any evidence of a public safety concern that would generate a need for hasty or significant revision of the current 510(k) process.**

A recent University of Minnesota study presented at the Institute of Medicine (IOM) meeting this past summer demonstrated that the history of medical device recalls shows no emerging problem with the device review process.[1] To date, FDA has not indicated a need for any 510(k) rescission; even in the highly controversial case of the ReGen 510(k), a panel review supported the issuance of the 510(k). Evidence shows that the process works to provide patients with safe and effective medical devices. A key FDA guidance, "*Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)*" issued in January 1997, has been helpful and frequently consulted by manufacturers for over ten years, resulting in cleared 510(k) submissions for tens of thousands of products with a solid history of safety and effectiveness. While specific examples within this guidance document may benefit from an update, the history of safety of Class II devices over the past decade shows that the basic concepts and algorithm in this and other 510(k) guidance documents and in 510(k) regulations work well and do not need major overhaul.

LSA has serious concerns about the manner in which 510(k) process improvements are being conducted and the possible ways in which the suggested changes might be implemented. FDA's request for comments on preliminary recommendations is unlike any of the regulatory changes that have taken place in the past decades. This is not an opportunity to comment on proposed regulation wording, or an opportunity to comment on the policy behind proposed guidance. We have been asked to comment on merely a list of concepts that FDA is considering, with no specific language or policy. These are not specific proposals, but rather topics for possible future action. Some topics, such as improved training for FDA staff, are not controversial and would likely generate broad public support. Other topics, however, could signal major changes in the manner in which medical devices reach the patient. In order for public comment to be a meaningful process, each substantive item should be subject to separate public comment after FDA has established specific proposed language or policy regarding the issue. Without a discussion of these specifics, the comment process is of little value.

LSA is also concerned that some of the recommendations are already being implemented within CDRH without public discussion, or even public notice. Changes in the acceptance of predicates, for example, have been made with no public announcement. We are concerned that the list of recommendations will lead to further silent adoption of new or changed policy within the Center.

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[1] Study results presented at IOM Meeting 3: Public Health Effectiveness of the FDA 510(k) Clearance Process, July 28, 2010; see http://www.iom.edu/~/media/Files/Activity Files/PublicHealth/510kProcess/2010-JUL-28/06 Hall.pdf

Each of the suggested changes could result in a positive impact that could help patients by fulfilling FDA's statutory mandate to take "appropriate action on the marketing of regulatory products in a timely fashion." On the other hand, each could be used in a manner to further slow down the 510(k) process and prevent US patient access to modern medical treatments. Each topic of discussion has the opportunity to add clarity and certainty to the process, but each also has the risk of adding layers of unneeded bureaucracy and delay.

Recommendation

LSA requests that these major changes in the 510(k) program be discussed and evaluated in an open public forum and not as part of internal FDA policy. Some should take the form of regulation, such as changes in the definition of intended use and indications for use. Some should be embodied in guidance, with an opportunity for public comment. None of the substantive changes should be undertaken within FDA out of the public eye and without public input.

LifeScience Alley (LSA) supports continued refinement of regulatory processes, in general, and supports modifications to the 510(k) process that improve efficiency. FDA's internal policies and practices are slowing down the 510(k) process. Through unneeded excess data demands FDA is creating a more burdensome process. FDA has created a new era of uncertainty, where no device company can predict how to get needed innovative medical devices to patients.

2. **LSA supports clarification of *Indications for Use* and *Intended Use* and requests that FDA use notice-and-comment rule making processes if proposing definitional changes in regulation to clarify these terms.**

LSA supports clarification of the definitions of *Indications for Use* and *Intended Use* and opposes combining the terms into one. Currently there are various existing regulatory definitions that would require formal notice-and-comment rulemaking to make any changes.

Intended Use and *Indications for Use* are defined as requirements for inclusion in market authorization submissions. Specifically, *Intended Use* is defined in the 510(k) regulation while *Indications for Use* is defined in the PMA regulation. While the definitions have some similarities, by policy and practice these terms have evolved different meanings and interpretations. FDA now requires that both be used in the 510(k) process.

Compare *Intended Use* in 21 CFR 807.92 for requirements for contents of a 510(k):

> A statement of the intended use of the device that is the subject of the premarket notification submission, including a general description of the diseases or conditions that the device will diagnose, treat, prevent, cure, or mitigate, including a description, where appropriate, of the patient population for which the device is intended.

...with *Indications for Use* in 21 CFR 814.20 for requirements for contents of a PMA:

> A general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.

Intended Use is defined by many FDA and regulatory experts as being more general than *Indications for Use*, and *Indications for Use* is thought of as more disease-specific. However, FDA requirements have appeared to require, without change to regulation or guidance, increasingly more specificity in both *Intended Use* and *Indication for Use.* No matter what definition is used, the term "general" appears to no longer be in effect. While the regulation requires that a 510(k) application include a statement of *Intended Use,* FDA also expects *Indications for Use* to be included in the 510(k) application and labeling. Then FDA issues a Substantial Equivalence letter for the 510(k), with an addendum attached, specifying *Indications for Use*.

Thus these two terms have evolved into the 510(k) process through practice and not by law. LSA believes that current concepts benefit public health and provide important policy distinctions but they should be more explicitly defined.

Recommendation

LSA recommends that FDA revisit the term "general" in the definitions and change its practice to follow the existing regulation. If this is achieved, LSA urges that FDA use the Good Guidance Policy to frame definitions upon which industry and FDA can agree. Since the current practices have no foundation in the regulations as they stand, LSA suggests that FDA use notice-and-comment rule making processes to update the regulations to conform to FDA practice.

3. **LSA supports clarification of the terms 'different technological characteristics' and 'different questions of safety and effectiveness', especially to clarify that whether a device raises 'different questions of safety and effectiveness' should be based on consideration of submitted data and other information.**

LSA recognizes the terminology inconsistencies between the statutory terms "different technological characteristics" and "different questions of safety and effectiveness," and the 510(k) guidance terms "new characteristics" and "new types of safety or effectiveness questions" and "new questions of safety and effectiveness." We agree that these inconsistencies could make it challenging to interpret the statutory review standard to determine when "different technological characteristics" raise "different questions of safety and effectiveness" when comparing the "technological characteristics" of a new device to those of a predicate. Terminology in FDA guidance could be clarified to use the same exact terms as the regulation

Industry and FDA reviewers generally have a practical and consistent understanding of what constitutes a 'different technological characteristic'. Table 5.2 in the 510(k) Working Group Preliminary Report and

Recommendations shows that, in response to the question "*Which of the following represent a change in the technological characteristics from the predicate device to the subject device? (Select all that apply.)",* ODE reviewers and managers selected the same items most of the time. The inconsistent terms have not resulted in poor 510(k) clearance decisions by the majority of FDA reviewers or poor 510(k) submissions by the majority of medical device companies. Industry and FDA reviewers have followed the guidance since 1997 and most cleared Class II medical devices have not been associated with a history of serious injury or failure to achieve their intended clinical use.

FDA 510(k) guidance is in agreement with 21 CFR 807; both require that the 510(k) submission —

- Establish that the subject and predicate devices have substantively the same intended use
- Compare technological features
- Provide data from testing and other analyses to demonstrate that the technological differences do not raise different questions of safety and effectiveness.

Recommendation

LSA believes there is a need to clarify that the determination of whether a device raises a different question of safety and effectiveness should be made after taking into account submitted data from testing and other analyses that address the technological differences. The following simple example illustrates this for the device in the case study, a powered dental hand piece:

- Both the air-powered and electrically powered devices are intended to cut, smooth, and polish tooth structure
- A feature comparison would reveal a technological difference in the means of powering the device.
- Electrical safety testing would be performed following standardized methods. The test results would be judged using industry standard acceptance criteria. The results would be considered in a risk assessment following industry standard risk management techniques. The conclusion would be that the risk of patient injury posed by the electric power source is acceptably low and not greater than the risk posed by the air power source.
- The electrically powered device would, therefore, have been shown to raise no different questions of safety and effectiveness, after taking into account the submitted test data and risk assessment summary.

A device that raises new questions of safety and effectiveness is one for which a rigorous, industry-standard risk assessment fails to result in a risk profile that is at least as low as the predicate device type. For example, a dental hand piece powered by a source for which there was no industry standard acceptance criteria or test method may raise new questions of safety or effectiveness (and therefore be a candidate for the de novo process).

4. LSA supports streamlining the de novo process and establishing a generic set of controls.

The possibility of streamlining and establishing a special set of product specific controls for devices classified into Class II through the de novo process may be beneficial to both industry and FDA. The legislative history of this provision contemplates a process that permits the FDA to reclassify certain low risk devices into Class I or II on the basis of established risk-based classification criteria when a new device is classified into Class III under the statute because there is no predicate device to which it can be found substantially equivalent. Congress included this section to limit unnecessary expenditure of CDRH and manufacturer resources that could occur if low risk devices were subject to premarket approval (PMA) under section 515. The section was not intended to significantly increase the number of NSE (not substantially equivalent) determinations or to otherwise alter the 510(k) provisions of the Act or CDRH's approach to the 510(k) classification process.[2]

Recommendation

LSA recommends streamlining the de novo process and establishing a special set of controls for devices undergoing the de novo process if the outcome includes the following:

- Use of the existing 513(g) process to establish a de novo classification and the type of supporting evidence needed to gain 510(k) clearance
- Guidance on —
    - Information to be included in a de novo 510(k) that the FDA will accept as evidence that the reasonable assurance of safety and effectiveness standard is met, and
    - How risk-based special controls can be implemented through performance standards, post-market surveillance, and/or patient registries, including guidelines for the submission of clinical data, possibly including OUS clinical data in premarket notification submissions in accordance with section 510(k)
- Elimination of the NSE review cycle allowing the de novo process to proceed more efficiently
- Allowing for product specific guidance, if needed, to be developed after completion of the initial de novo review process for a product type.

5. LSA generally supports better FDA understanding of a 510(k) device under review, but does not agree that any device should be available to FDA during future reviews.

LSA supports FDA access to a 510(k) device that is under review. However, as with all topics in the 510(k) Working Group Preliminary Report and Recommendations, the recommendation is broad and does not

[2] New Section 513(f)(2) - Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff Section 207 (FDAMA); Section 513 (f)(2) of the FDCA; 21 USC 360c(f)(2)

specify how FDA might access devices under review. LSA recommends that this requirement be more thoroughly specified and open to public comment before implementation.

Many devices are sufficiently small, (a catheter, for example) enabling a single device to be shipped to FDA during the review process for reference. However, shipping a large device, such as a computer imaging system console, to FDA would be impractical and expensive and FDA would not likely have appropriate accommodation. Units shipped to FDA would require secure area to store the devices, and electromedical equipment would require utilities. Considering that thousands of devices are reviewed by FDA annually, this would become a significant storage burden and cost for the agency. Likewise, it is simply not feasible for companies to be required to maintain physical specimens for some indefinite time period.

Instead, LSA recommends that FDA continue to implement and broaden their site visit program, whereby, for complex devices, the FDA review team visits the manufacturing site to see the device, how it is made, and how it works. In addition to site visits, FDA should continue to host "vendor days," providing the opportunity for manufacturers to bring their devices to FDA. Most manufacturers would prefer to demonstrate their device to the FDA review team to provide clarity and understanding to the product review process that may not be obtainable from pictures and diagrams of the device. For less complex products LSA believes an opportunity to present and discuss a device and its use with the FDA reviewer(s) using web meeting tools would greatly benefit the review. Manufacturers appreciate the challenges associated with not physically seeing and handling the device, and the benefit of having the reviewers get the "touch and feel" of the product. Questions are often received that could be resolved through a device demonstration. This approach could be administered by the FDA reviewer contacting the manufacturer within 30 days of the 510(k) submission and requesting a device demonstration, or by the submitter requesting an opportunity to demonstrate the device in the submission cover letter.

After a device is cleared for use, it should not be allowed to be examined in support of future reviews on behalf of other companies, regardless of whether it is cited as a predicate device. FDA would need to properly store these devices so that access would be available whenever another manufacturer cites the device as a predicate. This is impractical for the reasons mentioned above. Excessive handling of the device by FDA reviewers could damage the device by subjecting it to forces and movements for which the device was not designed. Although the recommendation suggests that manufacturers provide one device for FDA access, if the device is to be available during each review where it is cited as a predicate, it is inevitable that FDA would request or require additional units. Depending on the device, this could lead to an unnecessary expense for the manufacturer. A manufacturer should not be held responsible for the expense associated with the review of a competitor product.

Recommendation

In general, LSA supports FDA access to a 510(k) device that is under review. However, as with all topics in the 510(k) Working Group Preliminary Report and Recommendations, the recommendation is broad

and does not specify how FDA might access devices under review. LSA recommends that this requirement be more thoroughly specified before implementation. LSA does not support any requirement to maintain a physical specimen after clearance.

6. **LSA believes that Special Controls Guidance can continue to be used effectively, dynamically, and flexibly to communicate FDA's market authorization requirements for 510(k) devices, and that a new classification such as 'IIb' is unnecessary, overly complex and rigid.**

LSA recognizes the range of product complexity and risk profiles in the Class II category. LSA believes that FDA has successfully used Special Controls, such as guidance, to communicate its market authorization expectations for the variety of products in Class II with their inherent wide-ranging complexities and risk profiles. The use of guidance can continue to be used effectively, dynamically, and flexibly for this purpose. Establishing a new product category "IIb" would require the FDA to make rules regarding which devices fall into this sub-class; rules that may be outdated before long because neither the FDA nor industry can foresee new technologies currently undefined. General guidance for the totality of devices in a new class IIb category will likely be insufficient to result in submissions that satisfy the FDA; product-specific guidance will still be needed. LSA believes a new Class IIb category adds complexity with no value to the 510(k) review process.

Recommendation

LSA recommends that FDA develop guidance as an effective means to communicate current FDA expectations to industry; this allows the FDA more flexibility to keep up with innovative technologies. When needed, the guidance should specify the types of clinical data that could meet the definition of valid scientific evidence and would therefore be sufficient to demonstrate substantial equivalence. The need for clinical data should be based solely on whether there is field data indicating a safety concern for that technology or device type (e.g., infusion pumps). Various types of clinical evidence should be allowed, including: clinical data from published literature, single arm registry studies, treatment-only studies using published predicate data as a historical control, concurrent control trials, and proprietary clinical data that adequately addresses safety objectives.

7. **LSA believes the FDA lacks legal authority to dictate IDE study designs to sponsors and investigators as long as the design is safe and scientifically credible, but LSA is in favor of improving the efficiency of IDE reviews.**

LSA is concerned about the recommendation to "*continue efforts to improve the quality of the design….of clinical trials to support PMA's*" because no specific improvement efforts have been announced or communicated to industry using legally-defined communication mechanisms and accompanying public comment periods. In accordance with 21 CFR 812.30(b)(4), FDA lacks authority to disapprove IDE applications unless (i) the risks outweigh the benefits to the patient (i.e., patient safety), or (ii) the trial design is scientifically unsound. These criteria have been in place and utilized by trial

sponsors (both academic and industry) since shortly after the 1976 Medical Device Amendments to the Food, Drug, and Cosmetic Act. However, CDRH is apparently not currently approving IDE applications if the reviewers have concerns as to whether the trial will result in a PMA approval. This mandate appears to have resulted in virtually no new IDE applications being approved by ODE. This unilateral directive informally established a major additional criterion that has no regulatory basis. Further, this position is scientifically flawed in that it presumes that ODE personnel have the unique prescience to determine the outcomes of clinical research prior to the studies actually being executed and the data evaluated by the FDA and the medical community.

Recommendation

LSA recommends that FDA make public the legal analysis that supports its position on the criteria for approving IDE applications. If legal authority is not present, FDA should expediently approve IDE applications that are being delayed solely on the basis of the Director's informal directive. LSA also recommends that FDA feedback on study designs have a clear scientific basis, grounded in publically available, peer-reviewed scientific literature.

LSA applauds the FDA recommendations to analyze methods for improving the efficiency and effectiveness of the pre-IDE process and the IDE review process. LSA additionally lauds FDA for recommending an analysis of methods for meeting the statutory requirement of a complete review within 30 days. Current FDA practice seems to be a partial review of IDE applications, followed by a disapproval letter to the sponsor stating that the sponsor must acknowledge that FDA may find additional deficiencies as it continues its review of the IDE application. Perhaps the FDA has at times misdirected its IDE review resources trying to re-design trials for sponsors rather than focusing on the safety and scientific credibility of sponsors' study designs. LSA recommends that FDA follow current regulatory requirements in its review of IDE applications.

8. **LSA supports the continued use of multiple cleared devices in 510(k) submissions to establish substantial equivalence for technological advances in Class II devices.**

FDA has already begun an informal process of restricting multiple predicates in the determination of substantial equivalence. Thus, the reference to it in the FDA recommendations is not a new proposal, but a proposed formalization of practices already in place. LSA opposes a restriction on the use of multiple cleared devices, both in current practice and in future policies.

While there may be occasional cases of an unduly large number of predicates, LSA believes the use of multiple cleared devices is necessary to implement the statutory definition of substantial equivalence. In Section 513(i) the Food, Drug, and Cosmetic Act, the test for substantial equivalence has two elements: first, whether the device has the same intended use as the predicate and second, whether new technology is as safe and effective as the predicate and does not present new questions of safety and effectiveness. This second element may require additional evidence and the most common way to provide this has been to show safe and effective use of the technology in another legally marketed

device. The definition supports one of the most important development practices in Class II products: use of a technology proven on one type of device to improve a device with a different technology. To ban this practice would require new, useless, duplicative research to reprove concepts which are already known and have been cleared by FDA.

Recommendation

LSA urges caution in unnecessarily restricting the use of multiple cleared devices (to 5 or any other number) in that it will seriously threaten incremental technological advancements in Class II devices. Eliminating the use of multiple cleared devices would essentially rewrite the second element of Section 513(i), which cannot be done with guidance. FDA would be requiring essentially the same standard as for a PMA: original research.

Conclusion

LifeScience Alley supports continued refinement of regulatory processes, in general, and modifications to the 510(k) and IDE processes that improve efficiency. We look forward to an interactive and cooperative process by which industry and all other stakeholders will be notified of specific FDA proposals to change guidance or regulation and be given a reasonable opportunity to comment.

Sincerely,

Donald E. Gerhardt
President & CEO

[redacted]

Comments regarding the Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations

Docket No. FDA-2010-N-0348

I. INTRODUCTION

A. About the Coalition.

The coalition is a group of medical device sector stakeholders that support advancing patient health, encouraging medical device innovation and are committed to a strong, effective FDA. Our efforts are led by the **Medical Device Manufacturers Association** (MDMA), **Medical Imaging and Technology Alliance** (MITA), **California Healthcare Institute** (CHI), and **LifeScience Alley** (LSA). Our broader membership includes multiple stakeholders in the medical device sector, including small and large companies, inventors, investors, regional trade associations and more.

B. Guiding Principles for Reform.

We are committed to balanced, constructive, and well-informed engagement with FDA and other stakeholders to develop responsible reforms and advance patient benefit and medical innovation. The coalition is dedicated to ensuring that improvements made to the FDA's 510(k) review system follow these principles:

- Reforms must promote public health and protect patient safety;
- Reforms must support and enhance continued innovation of, and patient and provider access, to life-saving, life-enhancing medical technologies;
- Reforms to the system should be made after a fair and transparent process;
- Reforms should be based on sound science, data and evidence of need; and,
- Reforms should ensure that product reviews and regulation are conducted in a predictable, transparent, timely, resource-effective, and responsive manner.

II. PROCEDURAL RECOMMENDATIONS

We note that FDA has begun its reform effort admirably by reaching into its organization to solicit employee suggestions and by reaching out through town hall meetings and other mechanisms to seek initial stakeholder comment on its proposals. Under the leadership of Director Jeff Shuren, we anticipate and appreciate continued attention to transparency, stakeholder consultation, and sufficient notice and opportunity for comment. We would highlight several opportunities in this regard:

A. FDA should prioritize proposals and proceed sequentially.

We recommend that the FDA not attempt to implement at one time any significant subset of the proposals set out in the two reports. Rather, the coalition recommends that FDA solicit the public's sense of priorities and focus on those high-priority elements by making subsequent, detailed proposals, and providing additional notice and opportunity for comment. By prioritizing among the 200+ pages of proposals, stakeholders can then provide focused, detailed responses on the most likely agency actions. Such a process would conserve agency resources, reduce the burden on stakeholders, improve the quality and specificity of proposals and responses, and speed the completion of the 510(k) reform effort. Additionally, given the costs of the commissioned IOM 510(k) report, we urge the FDA to wait for those recommendations before evaluating any changes.

In setting the agency's priorities, FDA should consider the direct and societal cost of their proposals, including cost and burden on the agency, patients, manufacturers, and providers; and to consider the impact of delays in clearance, scuttled product development, reduced innovation, and lost jobs. Unwise changes have the very real possibility of increased cost of products, delayed/denied access to products, lost jobs, export of R&D, negative impact on the economy and adverse impact on the trade balance.

We do not believe that it is possible for the agency and industry to implement any significant number of the contemplated changes at the same time without bringing the system to a grinding halt. Prioritization is necessary to avoid such a collapse.

B. FDA should continue and expand transparency.

We recommend that FDA give stakeholders access to the FDA Task Force reports the agency used to prepare the Task Force recommendations. Doing so would enhance public comments, provide greater understanding of the agency's thought processes, issues, priorities, analytical methods and data, and be more in line with FDA and Administration transparency initiatives.

C. FDA should ensure further Notice and Comment on specific proposals.

The coalition and other stakeholders seek to work with the agency to develop improvements to the 510(k) system that strike the right balance of protecting patient safety and fostering innovation in an effective, efficient manner that minimizes unnecessary burden on the agency and industry. To do so, stakeholders need more specific, detailed recommendations on which to respond. Prior to publication of any final guidance,

regulation, or policy change, we urge that FDA go through a second round of notice and comment to receive feedback on specific, detailed proposals. Until finalization of any new guidance or regulations, the FDA ought to avoid "informal" adoption of any proposed changes.

D. FDA should exchange information and perspectives directly with stakeholders.

The coalition encourages FDA to consider engaging directly with stakeholders in real-time, in-person meetings to discuss reform proposals. For example, the coalition conceptually supports improvements in the de novo process. However, the August 4th proposals did not specify how the de novo process was to be improved. Process changes could either make the de novo process effective and efficient or could make it unworkable. Without knowing the specifics, all the coalition can do is to express its philosophical agreement with improving the de novo process. In addition, the de novo process reforms are potentially affected by other reforms in the proposals, notably reforms in the area of predicates. FDA would benefit most from stakeholder involvement that responds to specific proposals and that is delivered in face-to-face exchanges of information and perspectives; and not delivered in response to generalized proposals or delivered in sterile exchanges of written comments over long periods of time.

E. FDA should increase the time allowed for comments.

We recommend that FDA increase the amount of time during which comment on the proposals may be accepted. For the FDA to work through these complicated, interrelated concepts, the agency needed a year of analysis and 200+ pages of discussion. Indeed, the complexity of these issues is illustrated by the fact that it took FDA more than two months longer to issue the initial report than envisioned in the 2010 CDRH strategic plan. Given the complexity of the issues, the multi-dimensional aspects of all of them, and the significance of these proposed changes on patients, providers, industry stakeholders, payors, and investors, not to mention the agency itself, we believe that providing external groups a mere 60 days for comment on FDA's findings is unwise. A longer comment period would allow for more thoughtful input.

Moreover, no crisis exists that demands the FDA to make hasty decisions or take ill-informed action that risk causing unintended adverse effects. Additionally, asking for stakeholder comments on such major issues as creating new classes of devices within such a short time period seems unnecessary, as one would hope any final FDA recommendations be informed by the other bodies analyzing 510(k) reform options, namely the Institute of Medicine and Congress, which are operating on separate, longer timelines. All stakeholders should be concerned about serial changes to similar parts of the 510(k) system.

We urge FDA either to extend the comment period or make other provision for accepting, considering, responding to, and acting on those stakeholder comments.

III. KEY THEMES IN THE COALITION'S VIEW OF THE CDRH PROPOSALS

The coalition has assessed the various proposals found throughout the August 4th documents and combined our comments into common themes or categories. The coalition has not responded to each FDA proposal; on issues where we are silent, such should not be interpreted to indicate the coalition's support or opposition. Likewise, the coalition's support or opposition to broad concepts should not be taken as support or opposition to specific, detailed proposals advanced to implement the broad concepts. The details of implementation can substantially impact the workability of any proposal. We intend this to help provide a better understanding of both the broad areas of agreement and the interrelated nature of many of these proposed changes.

A. FDA must continue to ensure patient safety.

- Protection Against Fraud: The coalition supports FDA's authority to rescind specific 510(k)s obtained via fraud when appropriate to protect patients. Such FDA authority should not impact subsequent 510(k)s that utilize the subject predicate that were not fraudulently obtained, unless FDA finds under a 360(e)-type process that related devices present a significant public health issue.
- Limited Human Testing: Clinical testing on human patients should be limited to those situations where it is essential to provide data in order for the agency to make the relevant regulatory determination. When such clinical information is needed, the agency should look to all sources of clinical data, not just pharmaceutical style blinded, placebo controlled studies or similar types of clinical trials.

  Clinical data requirements should be limited to this small subset of 510(k) products, given the inherent risk that such testing poses to the human subject and the increase in cost, burden and time on both the sponsor and the agency. The agency should specify the limited requirements to submit clinical data.

  The coalition supports use of bench and non-clinical testing, and innovative and high-tech alternatives to experimental clinical testing on patients whenever possible and appropriate, and FDA should explicitly permit the use of clinical information from actual practice, literature, or other regulatory submissions.

  Research to date establishes that more human clinical testing does not increase product safety. Indeed, analysis of recent CDRH Class I recall data presented to IOM[1] indicate that 55% of recalls relate to post-market issues and thus are not prevented by additional human clinical trials. Of the recalls due to premarket issues, 75-80% of these are due to design issues, which illustrates the importance of improved QSR (design controls, etc) and not necessarily human clinical trials. Bench testing and design controls should be used to identify design issues without endangering patients or increasing the burden on the sponsor and the agency. Of

[1] R. Hall: Using Recall Data to Assess the 510(k) Process, IOM Public Meeting, July 28, 2010. http://www.iom.edu/~/media/Files/Activity%20Files/PublicHealth/510kProcess/2010-JUL-28/06%20Hall.pdf

the recall data analyzed, there were no recalls identified relating to newly discovered clinical risks, and only 7% of recalls were for inadequate labeling issues (potential surrogate description of newly discovered risks, but which also could include human factor issues). These data show that additional human clinical studies would have very little impact on Class I safety recalls. A second study presented to IOM also supports the above conclusions.[2]

- Expanded use of abbreviated and special 510(k)s: The coalition supports expanding the use of abbreviated and special 510(k)s in order to permit faster patient access and the allocation of FDA resources to more substantive submissions. Everyone benefits if resources are focused on the substantive questions. The coalition supports the current standard for when to submit a device modification for clearance.
- Unique Device Identification: The coalition supports the use of Unique Device Identification (UDI) for existing post market requirements. Tracking devices throughout the life of the product using UDI will enhance patient safety. However, industry input on the mechanics of implementation is needed before any such policy goes into effect.
- Off-Label Use: The coalition opposes any statutory changes involving off-label use. FDA currently has more than adequate enforcement powers relating to off-label matters. More significantly, this concept could limit the ability of physicians to act in the best interest of patients. As such, it is contrary to express statutory requirements that the agency not regulate the practice of medicine. It could also require companies to submit unnecessary information to FDA having nothing to do with the company's activities or objectives.

B. FDA should substantially maintain the current scope of the 510(k) system.

- Collective Effect of CDRH Proposals: The current set of proposals will, to the extent details are available and predictions can be made, in totality reduce substantially the number of products that will be eligible for review under the 510(k) system. Any change to the overall scope of the 510(k) must be made through statutory changes and not indirectly through a combination of multiple changes to varying parts of the process. While the agency's individual proposals will be discussed separately, FDA should consider and publically address the overall scope issue. FDA should make public the anticipated effect, if any, on the number of products eligible for 510(k) consideration for each proposal and for the total effect of all the proposals. This is necessary for stakeholders and policy makers to understand the overall effect of any change.

[2] W. Maisel: Premarket Notification: Analysis of FDA Recall Data, IOM Public Meeting, July 28, 2010. http://www.iom.edu/~/media/Files/Activity%20Files/PublicHealth/510kProcess/2010-JUL-28/05%20Maisel.pdf

It is also necessary for the agency to have a good understanding of the impact that substantial changes in scope may have on its own resource burdens; its ability to review products in a timely, predictable, and transparent way; and to understand the impact on stakeholders. The agency should be extremely cautious about making any dramatic shifts in scope for these practical reasons alone.

The coalition generally supports the notion that certain reforms are needed to improve the 510(k) system; however, the system should not be altered in such a way as to measurably reduce the number of products eligible for 510(k) clearance as such would limit patient access to life-saving, life-enhancing medical technologies and hamper innovation. (Similarly, the proposals should not substantially increase the number of products or product changes subject to 510(k) clearance, for example, by changing the exemption status of products or requiring submissions for modification to 510(k) products that do not current require a submission.) The coalition recognizes that a few specific product types might be up-classified or down-classified due to new information but we believe the overall scope of the program should remain as is.

- "Intended Use" and "Indications for Use:" FDA should not combine "intended use" and "indications for use." These terms reflect substantive differences and serve different purposes. "Intended use" is a statutory term (see, for example, 21 USC §360c(i)(1)(A)) and that statutory approach must be honored by all. Combining these terms will blur regulatory lines and force many products into new PMAs with no corresponding patient benefit. Combining these terms will lead to confusion over when filings are needed and cause delays in product reviews.

  Furthermore, the combination of these terms would require FDA to amend multiple prior regulations and guidance to reflect the new standards and terminology.

  The coalition recommends FDA explicitly define and distinguish (through rulemaking) the terms "intended use" and "indications for use" based on current statutory definitions and existing concepts. Any improved definitions should add clarity but not change or alter the existing definitions of these terms. FDA and all stakeholders should adhere to these definitions in all written material and decisions. The coalition believes all stakeholders could benefit from clearer guidance within existing statutory and regulatory bounds on the characteristics of "intended use" and "indication for use."
- Split Predicates: The coalition does not support the elimination, or significant limitations on, the use of split predicates. Split predicates are a valuable way to provide robust product reviews as information from different areas is brought to bear in the submission examination. The need for, and use of, split predicates reflects the nature of current health care practice. Combining already proven technologies permits better patient care and more efficient delivery of health care. Restricting the use of split predicates will hamper innovation and increase costs. Moreover, there is no statutory or regulatory basis to prohibit or limit split predicates.
- Multiple Predicates: The use of multiple predicates should not be restricted. Current practice (with improvements for administrative efficiency, predictability and certainty) properly permits the use of multiple predicates. Narrowing the scope of multiple

predicates hinders innovation, and products that utilize multiple predicates often provide improved patient care more efficiently. As the 510(k) system moves forward, more and more 510(k) cleared devices will exist that can serve as predicates. FDA should not encourage limiting the number of predicates brought to FDA's attention.

Along the same line, the coalition supports appropriate bundling of sufficiently similar products. Thus increases efficiency for both the agency and industry. It also permits more consistent product review. The coalition understands that bundling should not be permitted with dissimilar products.

- Functional Indications: FDA should consider increased utilization of functional indications as such indications are consistent with current medical practice and provide physicians with needed information and products which improve patient care. The use of functional indications is successful in other jurisdictions and supports the statutory prohibition on FDA becoming involved in the practice of medicine. Similarly, FDA should not limit the use of general indications or impose additional requirements on specific indications.
- 510(k) Flow-Chart: The coalition supports clarity in all guidance, including the 510(k) flow chart. The coalition encourages FDA to revise and update the 510(k) decision tree to give stakeholders more clarity on when 510(k) applications are appropriate, and when new applications are needed as a result of changes to products or indications. Efforts to clarify the flow chart should not be a disguised effort to limit the scope of the 510(k) system or to push any meaningful number of products from the 510(k) system into the PMA system. FDA should ensure that minor changes in products or uses do not trigger unnecessary submissions, as any such submission requirement ultimately means delays in getting the product to the patient. The coalition recommends FDA consider updating the flow-chart concept by beginning with four separate elements to be considered (predicate indications and intended use, technology, data requested) and then provide clear references to the data requirements and relevant guidance associated with each element. The coalition recommends FDA consider updating the flow-chart concept by beginning with four separate boxes (predicate, indications and intended use, technology, data request with references to the data requirements and relevant guidance associated with each element.

C. FDA should use product-specific controls, not create a new Class IIb.

- Authority and Rationale: Although there is some ambiguity in the FDA proposals over how FDA will approach possible Class IIb products, the coalition does not support the creation of a new Class IIb. First, FDA lacks the statutory authority to create a new class. Assuming the agency wants to create a Class IIb as a heuristic mechanism to solve some undefined problem, even this approach is flawed because, regardless of how the change is framed, the result would be the adoption of a new, broad set of requirements that apply across multiple different products, and that is the definition of a class. New classes require statutory authority, and the FDA obviously cannot avoid

this requirement by framing Class IIb as something less while accomplishing the same result. FDA cannot use guidance to create this new Class IIb.

Furthermore, the FDA has not shown that there is a group of 510(k) products that, as a class, require some additional requirements. FDA should set forth the data supporting the need for such a new classification before requesting public input on a specific proposal.

- Product-Specific Basis: The FDA should consider any new Class IIb-like requirements only after product-by-product consideration, as required by the statute, and as the most effective way to match requirements to products and therefore to effectively improve patient safety. Broad, automatic requirements based on classification rather than specific risk profiles and product characteristics would not effectively benefit patients, would disrupt innovation, and would delay patient access to products.

  The coalition understands that the agency may, on a case-by-case basis, have reason to demand specific, additional requirements for select products. The recent infusion pump initiative is an example of such a focused, directed activity. But class-wide special controls, as described by CDRH, are not an appropriate use of special controls. These should be – and are required to be – product-specific. The various specific requirements being considered for Class IIb are not value added. For example, there is no showing that requiring Class IIb-wide clinical data would be value added for many products that might be considered for inclusion in Class IIb. Likewise, there is no showing of any need to increase the number of submissions for which clinical data should be submitted. Analysis of 510(k) data establishes that the significant majority of post-clearance safety issues do not involve the absence of premarket clinical data. QSR systems are a better approach to improving product performance rather than requiring submission of non-value added clinical data.

- Consequences: We note that there is a substantial concern that there will be tendency to "up classify" devices into Class IIb and to place products going through the de novo process automatically into Class IIb. This tendency or approach must be avoided. Products must be individually assessed and assigned to product classifications based on established risk management principles.

- Workability: We note that tiering within existing classes historically has failed: FDA tried a form of tiering within classes in the 1990s when it assigned a tier 1, 2, or 3 designation to products within the various statutory classes. The tiers were intended, among other functions to help set priorities and analytical needs. By most accounts, and as reflected in the ending of this process in the late 1990s, the additional tiering efforts (and, creating a Class IIb is simply tiering within Class II) consumed unjustifiable time and effort, failed to keep up with innovation and changes in products, and resulted in difficult to sustain distinctions. Before proceeding further with the Class IIb concept, FDA should publicly discuss the 1990s effort at tiering and explain why this new Class IIb is somehow different and more workable.

D. FDA should ensure predictable, timely, efficient, and quality review process.

- Administrative Processes: The coalition supports improving the administrative processes used by FDA. The coalition agrees that improved databases that include more non-proprietary information would be beneficial for all stakeholders. This could include linkages between predicate devices and improved product codes. Certain information, such as 510(k) summaries, should be prepared with industry input to ensure accuracy and the protection of confidential information. Standardized electronic templates could also be useful. These administrative improvements, however, cannot be permitted to increase review times, decrease certainty or add burden without specific, demonstrated patient benefit exceeding this harm.
- Labeling: The coalition supports submission of final labeling provided that there is no "labeling review" that delays clearance or marketing. Likewise, CDRH already has access to all label modifications through inspections or subsequent submissions so CDRH should not require those not triggering a 510(k) submission requirement to be submitted to the agency. Requiring all minor label changes to be submitted adds nothing to patient safety and simply increases the burden on CDRH and industry.
- De Novo Process: The coalition supports a more effective, efficient, timely and predictable de novo process. To improve the de novo process, the coalition recommends FDA consider: 1) eliminating the need to go through the 510(k) (NSE) process prior to commencing the de novo process, 2) ensuring that classification decisions are based on legitimate risk assessments and the need to ensure patient access to new products, 3) creating defined time periods for key process steps, 4) creating a fast track de novo process for obvious Class II products and 5) eliminating the need to create new regulations or special controls unless needed on a case-by-case basis. FDA should ensure that data requirements are logical and relevant, and that the changes improve timeliness and predictability of review.

  The coalition recommends that FDA better define the de novo process and clarify the types of products and circumstances that can be handled under the de novo process. This should include specific time frames for each step in the process with FDA making public its performance compared to these time requirements. The coalition also suggests FDA consider use of a very general, no-guidance special control (e.g. for “clinical information” or "clinical data") and then later requiring a synopsis of the information actually used for the prior clearances. The coalition urges the FDA to ensure that changes do not result in an influx of submissions being subject to de novo as a result of reviewers finding that products are not exactly the same as the suggested predicate or, in conjunction with other Task Force proposals, result in de novo products being equated to PMA or a PMA-like pathway.
- Third Party Review System: The coalition supports the third party review system. It has proven to be an effective, efficient system to get low-risk products to patients faster and without burdening CDRH. The coalition urges FDA to establish clear guidance for when and how third party review is appropriate, to define the process for

reviewing third party recommendations in order to avoid duplicative reviews, to extend the scope of products that are eligible for such reviews, and to establish performance goals to promote better visibility FDA's performance and review times.

FDA should ensure that any changes do not result in more than a de minimis decrease in the number of products eligible for third party review and that FDA not put in place other obstacles to using third party review. The coalition is concerned with the existing perception that the agency will simply ask for clinical data in order to pull a product from third party review. Hopefully this perception is inaccurate but there should be clear guidance as to what products are eligible for third party review regardless of whether clinical information is submitted.

Likewise, the coalition supports increased training for CDRH and third party reviewers and increased access to information on other clearances (subject to protection of confidential information and appropriate handling of conflicts of interest).

- Ad hoc review teams: Additionally, the coalition supports the creation of ad hoc teams of experienced reviewers to provide temporary assistance to address backlogs and surges.
- Notices and Guidances: The coalition supports enhanced communication from CDRH to industry. However, CDRH should ensure that there is adequate public input before final guidance is promulgated. Excessive or improper use of "immediately effective" guidances or "notices to industry" raise administrative law issues and conflicts with good guidance practice requirements. The coalition supports transparency and public input and is very concerned that the "notice to industry" will bypass this important (and required) step. Transparency requires public disclosure of the proposed policy change and opportunity for public input to precede formal or informal implementation Going directly to “immediately effective” guidance or using "notices to industry" runs afoul to administrative law rules and transparency principles.

  The coalition believes guidance documents should to be prepared more quickly and draft guidances should not be allowed to remain in that status for long time periods.

  The coalition supports the drafting of proposed guidance by various stakeholders. For proposals which are particularly complex or will have a significant impact on patients, provides and the industry, there would be value in stakeholders having the ability to exchange information and perspectives on specific proposals face-to-face and not just through sterile, written exchanges of documents.
- Limitation on Use of Prior Predicates: Current FDA authority provides the agency with the ability to ensure that an unsafe product will not be marketed, regardless of existing predicates. As such, it is unclear whether there is a real need for a process to limit the use of a particular predicate. The coalition is not aware of any meaningful number of products cleared based on "bad" predicates.

  We specifically note that FDA currently has the statutory authority under 21 USC §360c(i)(2) to prevent a "bad" predicate from being the basis for a future clearance. Various procedural protections are built into the current system and will be needed if any new approach or process is adopted.

In any event, if such additional authority is sought, it may require statutory changes or at least new regulations; guidance alone is not sufficient to affect such important third party rights without rulemaking. Any such restriction on the use of an existing predicate must go through a public process at least similar to the existing 360e process.

- "Least Burdensome" Provisions: The coalition supports the statutory "least burdensome" requirement and earlier efforts to implement least burdensome in an effective manner throughout CDRH. CDRH should apply this requirement within the letter and spirit intended by Congress in 1997. It is inappropriate to translate "least burdensome" as "reasonably burdensome." Any guidance revision should ensure that least burdensome is applied and interpreted pursuant to the Congressional mandate.
- Quality of Submissions and the Use of Assurance Cases: The coalition supports high quality submissions and notes that CDRH has the authority to reject below-standard submissions. The coalition does not support the mandatory and widespread use of an assurance case methodology. Assurance cases are simply one method among many to assess product designs or predicate comparisons, and FDA has not demonstrated how assurance cases specifically will improve patient safety. FDA should not focus on any one method. Rather, CDRH and industry should use ISO 14971, other design validation systems and QSR concepts and provisions to select and implement the most appropriate method for the particular product, rather than follow a mandated, one-size-fits-all approach.
- Responding to New Science: The coalition supports the creation of a transparent Center Science Council and is interested is CDRH's views on improving processes for responding to new science. The coalition believes any process for responding to new science should include industry involvement with the identification and assessment of new scientific matters.

  The coalition awaits more detail on the responsibilities and processes of the new Center Science Council. It is unclear, for example, how the role of the Center Science Council will impact the current internal and external dispute resolution processes and the role of the ombudsman. The coalition does not support giving the Center Science Council authority to reverse decisions.

  In both the creation and the functioning of the Center Science Council, FDA must proceed carefully to ensure that all administrative law requirements are satisfied, and CDRH should make public, with an opportunity for stakeholder input, its initial proposals for this council's role, responsibility and processes. These administrative law requirements are especially important when considering the potential role(s) of the Center Science Council in product reviews and scientific debates. All stakeholders should have input into the processes, role, and responsibility of the new council.
- General Need for More Training: The coalition supports additional training at the various levels of the agency. A number of recommendations throughout the 200 pages of material point out the need for training. The survey of reviewers and management also confirms the need for training. If FDA staff does not understand the rules, then FDA is hard pressed to criticize industry for misunderstandings or mistakes.

- Science and Technology Training: The coalition supports additional training on relevant scientific and technical areas but urges FDA to focus training on those aspects that are relevant to FDA's statutory mission, processes and objectives. Too many times, someone at FDA has asked a question for personal curiosity rather than because the information is relevant to the review process. Training should seek to curb this problem and should be focused on what the individual needs to fulfill his or her statutory obligations.

  Industry and other stakeholders should be value added participants in such training. Reviewers should be encouraged to visit manufacturing facilities, research and engineering campuses, and relevant sites in the field, and learn firsthand about new technology, science, and technical matters. The coalition encourages FDA to consider a public-private training partnership to facilitate ongoing agency familiarity with the latest management techniques. FDA should also utilize academic, government and industry expertise to advise FDA on emerging scientific developments.
- Legal and Regulatory Training: As part of FDA's efforts to improve the 510(k) system , the coalition supports adequate training for FDA reviewers. Such training must include training on the legal requirements that bind both industry and FDA. Training must include rigorous instruction on legal and regulatory rules, processes and systems. As the internal survey demonstrated, too often FDA itself does not know the legal requirements. This leads to inappropriate questions and requests for information, incorrect and inconsistent decisions and uncertainty and delay. First and foremost, FDA is a legal regulatory and enforcement agency. FDA staff must understand those rules above all else.
- Standards Training: The coalition supports the use of consensus standards and supports training of reviewers on how to use such standards to avoid unnecessary work by either FDA or industry.

E. FDA should ensure that additional data requirements are justified by benefit to patients relative to burden.

- Use of Relevant Data: The coalition supports the use of data to improve the 510(k) process and ensure patient safety, including the submission of relevant, material and non-duplicative scientific information in appropriate situations. However, CDRH should not require excessive, duplicative, or non-value added submissions. There may well be thousands of articles relating to established and long-marketed products. CDRH should ensure that the relevant scientific information is provided to FDA without regard to source or format. Requiring "all" literature, for example, would unnecessarily burden FDA and industry for no added value. The coalition supports high quality clinical data in appropriate situations, but notes that "high quality clinical data" does not and should not necessarily mean clinical trials. CDRH should not require clinical data for the significant majority of 510(k) submissions. Review and assessment of clinical data issues and IDE challenges should include industry participation.

Furthermore, the agency currently has the statutory authority to require the submission of "information respecting safety and effectiveness" of the device at issue. See 21 USC §360c(i)(3)(A) and (B). It is unclear whether the agency requires any additional authority.

- Predicates as a Data Trigger: The simple fact of the number of predicates used should not trigger additional scrutiny. As time goes on, product submissions will have more and more predicates. In addition, FDA should not discourage companies listing multiple predicates as those listings can enhance FDA's review of the specific submission.
- Manufacturing Information: CDRH has generally no need nor the expertise for detailed manufacturing information. Other than increasing the burden on FDA and industry, there is no evidence to support the notion that agency review of manufacturing information would enhance product safety. As discussed below, even if CDRH creates a narrower group of Class IIb products, requiring manufacturing information will result in nothing more than increased review time, causing unnecessary delays in getting products to patients, and result in additional burden and costs on the agency and all other stakeholders.
- Physical Specimens: There is little agency benefit but much industry burden in forcing industry to maintain a physical specimen of all 510(k) products. For example, how would the agency appropriately handle highly expensive capital equipment or products with multiple iterations such as size differences? For products like imaging machines which are often very large (some are room sized) or certain products which must be stored in climate-controlled, stable environments, the physical specimen requirement would be incredibly burdensome in the short term, and unworkable in the long term. It is hard to imagine a situation in which the existence of a physical specimen would be of value to FDA years after product clearance. Stated differently, the existence of such specimens does not link to any statutory role of FDA.
- Device Modifications: The coalition does not support a requirement that all modifications, no matter how minor, be submitted to CDRH in some filing made every 3 years or so. First, there is long standing guidance that describes when a submission is needed for some change. That guidance properly separates significant modifications requiring a new clearance from minor modifications which do not. We also note the current regulatory system establishes that modifications should be submitted in cases in which the change could significantly affect safety or effectiveness. That standard should be maintained.

  Second, just because a company may not have applied that test correctly in the past is not the reason to force industry and the agency to deal with a flood of information.

  Third, FDA currently can learn about such changes in inspections and in subsequent submissions. A requirement that all modifications be submitted, even as part of an annual (or less frequent) report would burden FDA with meaningless changes and increase the burden on industry for no benefit. (We also note that the change would already have been made without FDA oversight and so this seems like closing the barn

door after the horse has left.) Furthermore, if the company did not make a submission as required, the agency can consider enforcement action.

Fourth, the agency's expressed concern is that companies are implementing modifications without necessary clearances, but if a company is going to break the law (deliberately or inadvertently), requiring some filing 2-3 years later wouldn't make a difference.

Finally, by the time the report goes to the agency, the feared change will have already been made and be on the market for a substantial time. Any such requirement along the lines suggested simply doesn't address the issue raised by the agency.

Perhaps the answer lies elsewhere. QSR systems are in place to ensure that changes are assessed and validated. Likewise, including literally all modifications in a submission adds burden for no benefit. At the very least, any such new obligation must include a de minimis level. The coalition believes submissions should include only relevant or material changes from the predicate device; there is no reason to require anything more.

- "Conditions of Clearance:" CDRH currently has more than adequate post market requirements including special controls (see 21 USC §360c(a)(1)(B) and 522 orders. The agency neither has the need nor the authority to create "conditions of clearance." Given the predicate-based 510(k) system, such an approach would not add any value and would not link products and clearances with relevant post market data. Despite the futility, even if FDA wanted to adopt a "conditions of clearance" approach such a change would require statutory authority.

F. FDA should ensure reasonable public access and transparency in the 510(k) system.

- Public Metrics: The coalition strongly supports the creation of relevant public metrics relating to the performance of the 510(k) system. These metrics should include measures of whether various submission requirements enhance patient safety and benefit as well as time periods (by division, branch or other subset) for actual FDA review time and for total cycle time including industry time. To the extent that gaps are noted in performance or value, CDRH should take steps to address the issues. This must also include specific periodic review of regulatory requirements that should be eliminated if they are determined not to be relevant to patient safety and effectiveness. The coalition recommends the joint development of metrics to ensure regular and timely communication between the agency and stakeholders.
- Transparency of Applicant Information: The coalition supports clarity in submissions including placing information currently required in a 510(k) submission into a single section. Likewise, high level schematics or photos may have a place in submissions if they aid in review. These should be for internal, FDA-use only and not be made public, as such could implicate trade secrets.
- Transfers of ownership: The coalition sees value in disclosing to FDA transfers of ownership from one company to another and eventual posting on FDA's website.

This requirement must be timed so as not to prematurely disclose highly confidential corporate transactions such as acquisitions.

- Transparency of FDA Information: The coalition supports bi-directional disclosure of information given to and provided from the agency. We urge the FDA to improve transparency and efficiency throughout the review process by using information technology to, e.g. track review status and report on outcomes; improve the content of and search capabilities in the 510(k) database, the product code database, the recall database, and the guidance document database; incorporate standardized data elements in databases beyond current high-level categories in order to improve functionality and accuracy of these data bases. The coalition also recommends FDA publicly discloses all new or modified requirements (data or other requirements) to enhance stakeholders' knowledge and certainty of data requirements. Additionally, the coalition supports public audits of the 510(k) system, and recommends that industry input be part of any audit. Patients, providers, patients, providers, industry stakeholders, payors, investors, and the agency all benefit from increased transparency of FDA information.
- Accessing Experts: The coalition is interested in how CDRH would address confidentiality, conflict of interest and FACA issues inherent in using social media to access various experts. Additional information on this proposal is needed before the coalition is in a position to fully assess the proposal and offer informed views.

IV. CONCLUSION

The coalition supports a strong 510(k) system that advances public health, patient access to innovation products and predicable, transparent processes. FDA must ensure that the 510(k) reform process itself is done in a deliberative, thoughtful, way that includes assessment of public health, innovation and predictability. As the 510(k) reform process moves forward, the agency needs to provide adequate time for input and additional notice and comment opportunities for each specific proposal. CDRH should consider engaging directly with stakeholders in real-time, in-person meetings to discuss reform proposals. Throughout the process, CDRH must follow its current statutory authorities and ensure compliance with administrative law rules. Any requirement (old or new) should not be maintained unless it materially advances the statutory purpose of CDRH. We urge the FDA to explicitly consider, debate and balance FDA's twin purposes of protecting patients and fostering innovation at every turn.

Respectfully submitted,

Mark Leahey

Medical Device Manufacturers Association (MDMA)

mleahey@medicaldevices.org
(202) 354-7174

David Fisher
Medical Imaging and Technology Alliance (MITA)
dfisher@medicalimaging.org
(703) 841-3279

Todd Gillenwater
California Healthcare Institute (CHI)
gillenwater@chi.org
(202) 974-6313

Don Gerhardt
LifeScience Alley (LSA)
dgerhardt@lifesciencealley.org
(952) 746-3822

Joe Trauger

Vice President
Human Resource Policy
National Association of Manufacturers

Randel K. Johnson

Senior Vice President
Labor, Immigration, & Employee Benefits
U.S. Chamber of Commerce

October 4, 2010

The Honorable Dr. Margaret Hamburg
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

RE: Docket No. FDA-2010-N-0348: Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations; Availability; Request for Comments

Dear Dr. Hamburg:

The National Association of Manufacturers and the U.S. Chamber of Commerce, appreciates the opportunity to comment on the preliminary report and recommendations of both the Center for Devices and Radiological Health 510(k) Working Group and the Task Force on the Utilization of Science in Regulatory Decision Making. Signatories to this letter, trade associations representing the interests of businesses, small and large, from all sectors of the economy employing tens of millions of Americans, as well as the medical device industry, strongly believe that an appropriate balance should be struck between government regulation and free enterprise. We are committed to working with the FDA to ensure that private industry is not adversely affected by the recommendations issued in these reports.

Our organizations are deeply committed to policies that will support a vibrant and successful manufacturing sector—a critical ingredient in U.S. economic growth and standards of living. The medical technology industry, comprising manufacturers of medical devices and diagnostics, is a sector of manufacturing where the U.S. leads the world. This industry represents the eleventh largest manufacturing sector in terms of exports, and is one of the few manufacturing sectors that has consistently maintained a favorable balance of trade. The sector, like other manufacturing industries, provides jobs that substantially exceed U.S. average wages and is an engine for jobs in supporting manufacturing and service industries. The prosperity that the medical technology industry brings to many American workers is dependent on an FDA review process that assures efficient and consistent reviews, while protecting patients against unsafe or ineffective products.

Current trends in FDA review of 510(k) products show a troubling pattern of inefficiency and larger burdens on manufacturers that threaten American manufacturing leadership in this vital sector. Whether the issue is total review times, the number of review cycles, the amount of time manufacturers spend answering FDA questions after products are submitted for review, or the withdrawal of applications before a final decision, FDA statistics show performance has declined

substantially since 2003, despite the significant additional resources that the FDA has received from expanded user fees and appropriations.[1]

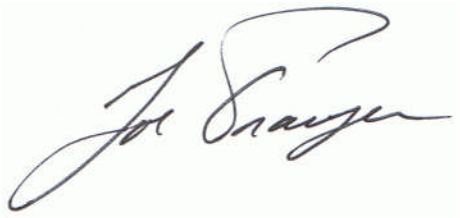
At the same time, the current 510(k) process has an exemplary safety record that does not demonstrate a case for sweeping reforms that would add to manufacturers' burdens in developing products and securing FDA approval. Recent studies by the Battelle Memorial Institute,[2] Professor Ralph Hall of the University of Minnesota[3], and Dr. William Maisel of the Medical Device Safety Institute at the Beth Israel Deaconess Hospital in Boston[4] have all demonstrated that only a very small proportion of approved 510(k) products subsequently show safety problems.

With this backdrop, the National Association of Manufacturers and the U.S. Chamber of Commerce are concerned that many of the proposals developed by the 510(k) working group undermine U.S. manufacturing employment, growth, and competitiveness while not significantly increasing the protection of public health. Our organizations urge the FDA to reject proposals, such as imposing arbitrary limits on acceptable predicates, redefining the term substantial equivalence, and eliminating the separate classification of intended use and indications for use, that alter basic aspects of the current program. These proposals will increase development time as well as costs for manufacturers substantially without a demonstrated need for these additional burdens. Additionally, these proposals could worsen public health by depriving patients of timely access to new treatments and cures. Changes that will increase approval difficulty or time should only be proposed for product types where there is a demonstrated need for additional requirements.

At the same time, we urge FDA to implement proposals on a priority basis that will address the current problems with the review process, including better training of reviewers and managers, and the issuance of more guidance documents.

Finally, FDA should consider the capacity of an already stressed system to absorb additional changes. With more than 50 changes proposed by the task force, any attempt to implement a large proportion of them rapidly would create confusion and necessitate retraining of reviewers and manufacturers that could be extremely destructive to the review process for many years.

Sincerely,



Joe Trauger
Vice President
Human Resource Policy
National Association of Manufacturers

Randel K. Johnson
Senior Vice President
Labor, Immigration, & Employee Benefits
U.S. Chamber of Commerce

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[1] FDA statistics: FDA 510(k) Working Group, *Preliminary Report and Recommendations*, Center for Devices and Radiological Health, U.S. Food and Drug Administration, August, 2010.

[2] Battelle: Battelle Memorial Institute, "510(k) PreMarket Notification Evaluation," September, 2010.

[3] Hall, Ralph F. Hall, "Using Recall Date to Assess the 510(k) process," University of Minnesota, Institute of Medicine 510(k) workshop, July 28, 2010.

[4] Maisel: William H. Maisel, M.D., "Premarket Notification: Analysis of FDA Recall Data," Institute of Medicine 510(k) workshop, July 28, 2010.

701 Pennsylvania Avenue, Ste. 800
Washington, DC 20004–2654
Tel: 202 783 8700
Fax: 202 783 8750
www.AdvaMed.org

AdvaMed
Advanced Medical Technology Association

October 4, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2010-N-0348: Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations; Availability; Request for Comments

Dear Sir/Madam:

The Advanced Medical Technology Association (□AdvaMed□) is pleased to provide the enclosed comments and recommendations on the Center for Devices and Radiological Health *510(k) Working Group Preliminary Report and Recommendations* and the *Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations.*

AdvaMed represents manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatments. Our members produce nearly 60 percent of the health care technology purchased annually in the United States. These members range from the smallest to the largest medical technology innovators and companies. Nearly 70 percent of our members have less than □30 million in sales annually.

AdvaMed appreciates the opportunity to comment.

Sincerely,

Janet Trunzo
Executive Vice President
Technology and Regulatory Affairs

Attachments

AdvaMed
Advanced Medical Technology Association

Comments and Recommendations on
Center for Devices and Radiological Health
510(K) Working Group Preliminary Report and Recommendations
Task Force On The Utilization of Science in Regulatory Decision Making
Docket No. FDA-2010-N-0348

Submitted by:
Advanced Medical Technology Association (AdvaMed)

October 4, 2010

AdvaMed
Advanced Medical Technology Association

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ATTACHMENTS

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Advanced Medical Technology Association

General Comments

AdvaMed commends the 510(k) Working Group (the Working Group) and the Task Force on the Utilization of Science in Regulatory Decision Making (the Task Force) on their thorough review and evaluation of the 510(k) program and the use of science. AdvaMed supports the Working Group's stated goals of the 510(k) program to "(1) assure, through a quality review process, that marketed devices, subject to general and applicable special controls, provide a reasonable assurance of safety and effectiveness; and (2) "fostering innovation in the medical device industry" and the Task Force's stated goal of making recommendations to CDRH "on how the Center can quickly incorporate new science "including evolving information, novel technologies, and new scientific methods "into its decision making, while also maintaining as much predictability as practical."

AdvaMed also supports many of the concepts outlined in the proposals or elements of the proposals (contingent upon their appropriate implementation under existing statutory authority) contained in the two reports (see our more detailed specific comments below) that we believe will enhance and improve program predictability. These include among others: improving the training and education of reviewers; streamlining the implementation of the *de novo* classification process; establishing collaborative relationships to better leverage external scientific expertise; establishing a Center Science Council to provide oversight and consistency across reviews; posting of reviewer decision summaries and a webpage for new information; a standard template for 510(k) summaries; and documentation of 510(k) ownership transfer.

Nonetheless, we are concerned that the cumulative effect of the multiple CDRH proposals in the two reports would result in a revolutionary change in both the 510(k) process and in the larger regulatory framework and may adversely affect the ability of CDRH to effectively carry out mission-critical functions, including timely reviews. Wholesale changes to the program will also impact industry's ability to efficiently bring new devices to market.

AdvaMed believes proposed changes to the program must also be considered within two important parameters. First, the program as a whole has an admirable safety record. Recent, independent studies by Dr. William Maisel of the Medical Device Safety Institute at the Beth Israel Deaconess Medical Center, Professor Ralph Hall of the University of Minnesota, and Battelle Memorial Institute all show an extremely low rate of recall of medical devices and diagnostics because of safety problems. The Battelle Memorial Institute report is provided in Attachment A.

Second, as documented in the body of the report, there has been a significant deterioration in the efficiency and consistency of the 510(k) review process. If these trends are not reversed, there will be a long-term negative impact on patient access to new and improved treatments and to investment by and in device companies and others in the development of new products. Key statistics demonstrating these points include:[1]

[1] Statistics derived from ODE Annual Performance Reports and FDA's 510(k) report (page 39).

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- The average total 510(k) decision time has risen 20 percent (97 days in 2002 vs. 116 days in 2008)
- The number of days 510(k) submitters spend answering FDA requests for more data has nearly tripled (19 days in 2002 vs. 51 days in 2008)
- The number of review cycles (the number of times FDA "stops the clock" on its review because it has decided to ask the manufacturer for more information) per 510(k) application increased by one-third between 2002 and 2008 (1.4 per application in 2002 vs. 1.9 in 2008)
- The percentage of 510(k)s withdrawn by sponsors has skyrocketed 89 percent from 2004 to 2009 (nine percent to 17 percent).

Importantly, the 510(k) report establishes that review staff fails to consistently interpret regulatory requirements. This suggests that there may be two over-arching root causes leading to inconsistent interpretations: (1) review staff may not be effectively trained; and (2) the guidances they follow are not sufficiently clear. Changes to the existing system will not constitute an improvement unless these root causes are first addressed. CDRH should consider whether improved training, clearer guidances, and guidance development would eliminate the need for some of the proposed changes to the program.

We also urge CDRH to establish clear program metrics. Although the 510(k) and science program reviews were thorough, without established program metrics, some of the proposed changes may be intended to correct problems based on a few outliers or anecdotes when resources could be better targeted elsewhere.

Once the impact of improved training and improved guidance has been assessed, and clear program metrics have been established, AdvaMed recommends that CDRH prioritize and implement a limited number of selected recommendations on which there is general agreement. Once these have been implemented, additional recommendations on which there is agreement can be launched and implemented. A process that tries to implement too many changes at once would overwhelm CDRH, its reviewers and industry, and likely will not lead to improvement. AdvaMed has specific recommendations for those proposals that should be implemented on a priority basis:

- Establishment of a Center Science Council to ensure consistency and predictability in conjunction with metrics to assess whether the new process is effective.
- Revision of the existing guidance to streamline the implementation of the *de novo* classification process and to clarify evidentiary expectations for *de novo* requests.

The table below also outlines at-a-glance the AdvaMed position on each of the 510(k) Working Group and Utilization of Science in Regulatory Decision-making recommendations and sub-proposals within the recommendations. In each case, we have stated whether AdvaMed "supports," "supports with modifications," or "does not support" the recommendation and the basis for our position. Below, please find our specific comments on each of the CDRH recommendations.

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SUMMARY OF ADVAMED POSITIONS ON WORKING GROUP□TASK FORCE RECOMMENDATIONS

CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
510(k) Report			
The 510(k) Working Group recommends that CDRH revise existing guidance to consolidate the concepts of □indication for use□and □intended use□into a single term, □intended use,□in order to reduce inconsistencies in their interpretation and application. Several public comments expressed concern that, if these two terms were combined, any proposed change in a device□s label indications could be considered a change in □intended use.□ The Working Group recognizes the importance of providing submitters with the flexibility to propose certain changes to their labeling, without such a change necessarily constituting a new □intended use.□ Therefore it recommends that CDRH carefully consider what characteristics should be included under the term □intended use,□so that modifications that are currently considered to be only changes in □indications for use□and that CDRH determines do not constitute a new □intended use,□are not in the future necessarily construed as changes in □intended use□merely because of a change in semantics. Any change in terminology would be intended to provide greater clarity and simplicity, not necessarily to make the concept of □intended use□more restrictive.		✓ Revise existing guidance to *clarify* each term, *not consolidate* terms.	✓
The Center should also carefully consider what it should call the existing □Indications for Use□statement in device labeling and the □Indications for Use□form currently required for all 510(k)s, in order to avoid confusion in terminology but still maintain an appropriate level of flexibility for submitters.		✓ Include indications for use in *labeling* but not *label.*	
The 510(k) Working Group recommends that CDRH develop or revise existing guidance to clearly identify the characteristics that should be included in the concept of □intended use.□		✓ Revise existing guidance to *clarify* each term, *not consolidate* terms.	
The 510(k) Working Group further recommends that CDRH provide training for reviewers and managers on how to determine □intended use.□Such training should clarify the elements of a device application that should be considered when determining the □intended use,□e.g., product labeling, device design (explicit or implied), literature, and existing preclinical or clinical data. Training on □intended use□should also be provided to industry.		✓ Reviewers should be trained on how to determine *each* term.	
The 510(k) Working Group recommends that CDRH explore the possibility of pursuing a statutory amendment to section 513(i)(1)(E) of the Federal, Food, Drug and Cosmetic Act ... that would provide the agency with the express authority to consider an off-label use, in			✓

CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
certain limited circumstances, when determining the intended use of a device under review through the 510(k) process.			
The 510(k) Working Group recommends that CDRH reconcile the language in its 510(k) flowchart (shown on page 27 of this report) with the language provided in section 513(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360c(i) regarding different technological characteristics and different questions of safety and efficacy.			✓
The 510(k) Working Group recommends that CDRH revise existing guidance to provide clear criteria for identifying different questions of safety and effectiveness and to identify a core list of technological changes that generally raise such questions (e.g., a change in energy source, a different fundamental scientific technology).		✓ Identifying new types of safety and effectiveness questions	
The 510(k) Working Group further recommends that CDRH develop and provide training for reviewers and managers on how to determine whether a 510(k) raises different questions of safety and effectiveness. Training on different technological characteristics and different questions of safety and effectiveness should also be provided to industry.		✓ Identifying new types of safety and effectiveness questions	
The 510(k) Working Group recommends that CDRH consider developing guidance on when a device should no longer be available for use as a predicate because of safety and/or effectiveness concerns. It is expected that such a finding would be an uncommon occurrence. Any factors set forth in guidance regarding when a device should no longer be used as a predicate should be well-reasoned, well-supported, and established with input from a range of stakeholders, and unintended consequences should be carefully considered.			✓
The 510(k) Working Group recommends that CDRH consider issuing a regulation to define the scope, grounds, and appropriate procedures, including notice and an opportunity for a hearing, for the exercise of its authority to fully or partially rescind a 510(k) clearance. As part of this process, the Center should also consider whether additional authority is needed.			✓
The 510(k) Working Group recommends that CDRH develop guidance on the appropriate use of more than one predicate, explaining when multiple predicates may be used.		✓ Support guidance on use of multiples with no limitation on the number allowed.	
The Center should also explore the possibility of explicitly disallowing the use of split predicates.			✓
In addition, CDRH should update its existing bundling guidance to clarify the distinction between multi-parameter or multiplex devices (described in Section 5.1.2.3 of this report) and bundled submissions (described in Section 4.3.4.2).		✓ Only to clarify the distinction between multi-parameter or	

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
		multiplex devices	
The 510(k) Working Group recommends that CDRH provide training for reviewers and managers on reviewing 510(k)s that use "multiple predicates," to better assure high-quality review of these often complex devices. The training should clarify the distinction between multi-parameter or multiplex devices and bundled submissions. In addition, CDRH should more carefully assess the impact of submissions for multi-parameter or multiplex devices and bundled submission on review times, and should consider taking steps to account for the additional complexity of these submissions as it establishes future premarket performance goals.	✓		
The 510(k) Working Group further recommends that CDRH conduct additional analyses to determine the basis for the apparent association between citing more than five predicates and a greater mean rate of adverse event reports, as shown in Section 5.1.2.3 of this report.			✓
The 510(k) Working Group recommends that CDRH revise existing guidance to streamline the current implementation of the de novo classification process and clarify its evidentiary expectations for de novo requests. The Center should encourage pre-submission engagement between submitters and review staff to discuss the appropriate information to provide to CDRH for devices eligible for de novo classification, potentially in lieu of an exhaustive 510(k) review. The Center should also consider exploring the possibility of establishing a generic set of controls that could serve as baseline special controls for devices classified into class II through the de novo process, and which could be augmented with additional device-specific special controls as needed.	✓		
The 510(k) Working Group recommends that CDRH revise existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k), and, for those modifications that do warrant a new 510(k), what modifications are eligible for a Special 510(k).	✓		
The 510(k) Working Group further recommends that CDRH explore the feasibility of requiring each manufacturer to provide regular, periodic updates to the Center listing any modifications made to its device without the submission of a new 510(k), and clearly explaining why each modification noted did not warrant a new 510(k). The Center could consider phasing in this requirement, applying it initially to the "class IIb" device subset described in Section 5.2.1.3, below, for example, and expanding it to a larger set of devices over time.			✓
The 510(k) Working Group recommends that CDRH consider adopting the use of an "assurance case" framework for 510(k) submissions. An "assurance case" is a formal method for demonstrating the validity of a claim by providing a convincing argument together with supporting evidence. It is a way to structure arguments to help ensure that top-level claims are credible and supported. If CDRH pursues this approach, the Center should develop guidance on how submitters should develop and use an assurance case to			✓

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
make adequate, structured, and well-supported predicate comparisons in their 510(k)s. The guidance should include the expectation that all device description and intended use information should be submitted and described in detail in a single section of a 510(k). The guidance should also clearly reiterate the long-standing expectation that 510(k)s should describe any modifications made to a device since its previous clearance. CDRH should also develop training for reviewers and managers on how to evaluate assurance cases.			
The 510(k) Working Group further recommends that CDRH explore the possibility of requiring each 510(k) submitter to provide as part of its 510(k) detailed photographs and schematics of the device under review, in order allow review staff to develop a better understanding of the device□s key features. Currently, CDRH receives photographs or schematics as part of most 510(k)s; however, receiving both as a general matter would provide review staff with more thorough information without significant additional burden to submitters.			✓
Further, CDRH could include photographs and schematics, to the extent that they do not contain proprietary information, as part of its enhanced public 510(k) database, described below, to allow prospective 510(k) submitters to develop a more accurate understanding of potential predicates. Exceptions could be made for cases in which a photograph or schematic of the device under review will not provide additional useful information, as in the case of software-only devices.			✓
CDRH should also explore the possibility of requiring each 510(k) submitter to keep at least one unit of the device under review available for CDRH to access upon request, so that review staff could, as needed, examine the device hands-on as part of the review of the device itself, or during future reviews in which the device in question is cited as a predicate.			✓
The 510(k) Working Group recommends that CDRH provide additional guidance and training for submitters and review staff regarding the appropriate use of consensus standards, including proper documentation with a 510(k).	✓		
CDRH should also consider revising the requirements for □declaration of conformity□with a standard, for example by requiring submitters to provide a summary of testing to demonstrate conformity, if they choose to make use of a □declaration of conformity.□			✓
The 510(k) Working Group recommends that CDRH should consider revising 21 CFR 807.87 to explicitly require 510(k) submitters to provide a list and brief description of all scientific information regarding the safety and/or effectiveness of a new device known to or that should be reasonably known to the submitter. The Center could then focus on the listed scientific information that would assist it in resolving particular issues relevant to the 510(k) review.			✓
The 510(k) Working Group recommends that CDRH develop guidance defining a subset of class II devices, called □class IIb□devices, for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting, would typically be			✓ (See AdvaMed proposal for

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
necessary to support a substantial equivalence determination.			subset of Class II.)
The 510(k) Working Group further recommends that CDRH develop and implement training for review staff and industry regarding the delineation between class IIa and class IIb.			✓
The 510(k) Working Group recommends that CDRH, as part of the class IIb guidance described above, provide greater clarity regarding the circumstances in which it will request clinical data in support of a 510(k), and what type and level of clinical data are adequate to support clearance. CDRH should, within this guidance or through regulation, define the term clinical data to foster a common understanding among review staff and submitters about types of information that may constitute clinical data. General recommendations related to the least burdensome provisions, premarket data quality, clinical study design, and CDRH s mechanisms for pre-submission interactions, including the pre-IDE and IDE processes, are discussed further in the preliminary report of the Center s Task Force on the Utilization of Science in Regulatory Decision Making (described further in Section 2, below). That report also recommends steps CDRH should take to make well-informed, consistent decisions, including steps to make better use of external experts.		✓ Support greater clarity of circumstances and definition of clinical data. Do not support Class IIb category. All IVD s should not be placed in Class IIb.	
The 510(k) Working Group recommends that CDRH explore greater use of its postmarket authorities, and potentially seek greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices. If CDRH were to obtain broader authority to require condition-of-clearance studies, the Center should develop guidance identifying the circumstances under which such studies might be appropriate, and should include a discussion of such studies as part of its class IIb guidance.		✓ Support exploring *current* authority	✓ Do not support *expanding* postmarket authority
The 510(k) Working Group further recommends that CDRH continue its ongoing effort to implement a unique device identification (UDI) system and consider, as part of this effort, the possibility of using real-world data (e.g., anonymized data on device use and outcomes pooled from electronic health record systems) as part of a premarket submission for future 510(k)s.		✓ Premature to consider submission of data from electronic records.	
The 510(k) Working Group recommends that CDRH develop guidance to provide greater clarity regarding what situations may warrant the submission of manufacturing process information as part of a 510(k), and include a discussion of such information as part of its class IIb guidance.		✓ Should apply to only a small subset; should be summary information only; should not include IVD products.	
The 510(k) Working Group further recommends that CDRH clarify when it is appropriate to use its authority to withhold clearance on the basis of a failure to comply with good manufacturing requirements in situations where there is a substantial likelihood that such failure will potentially present a serious risk to human health . . .		✓ Clarify when it is appropriate to use its current authority and incorporate due process with manufacturer s input.	

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
. . . and include a discussion of pre-clearance inspections as part of its □class IIb□guidance.			✓ Do not support preclearance inspections.
The 510(k) Working Group recommends that CDRH develop guidance and Standard Operating Procedures (SOPs) on the development and assignment of product codes, in order to standardize these processes and to better address the information management needs of the Center□s staff and external constituencies.	✓		
510(k) Working Group further recommends that CDRH enhance existing staff training on the development and assignment of product codes.	✓		
The 510(k) Working Group recommends that CDRH develop a publicly available, easily searchable database that includes, for each cleared device, a verified 510(k) summary, photographs and schematics of the device, to the extent that they do not contain proprietary information, and information showing how cleared 510(k)s relate to each other and identifying the premarket submission that provided the original data or validation for a particular product type.		✓ Photographs and schematics should not be included in the public database.	
The 510(k) Working Group recommends that CDRH develop guidance and SOPs for the development of 510(k) summaries to assure they are accurate and include all required information identified in 21 CFR 807.92. The Center should consider developing a standardized electronic template for 510(k) summaries.	✓		
The 510(k) Working Group recommends that CDRH revise existing regulations to clarify the statutory listing requirements for submission of labeling. CDRH should also explore the feasibility of requiring manufacturers to electronically submit final device labeling to FDA by the time of clearance or within a reasonable period of time after clearance, and also to provide regular, periodic updates to device labeling, potentially as part of annual registration and listing or through another structured electronic collection mechanism. If CDRH adopts this approach, updated labeling should be posted as promptly as feasible on the Center□s public 510(k) database after such labeling has been screened by Center staff to check for consistency with the device clearance. In exploring this approach, CDRH should consider options to assure that labeling could be screened efficiently, without placing a significant additional burden on review staff. For example, to allow for more rapid review of labeling changes, the Center could consider the feasibility of requiring manufacturers to submit a clean copy and a redlined copy of final labeling and subsequent updates, highlighting any revisions made since the previous iteration. As a longer-term effort, the Center could explore greater use of software tools to facilitate rapid screening of labeling changes. The Center should consider phasing in this requirement, potentially starting with only a subset of devices, such as the □class IIb□device subset described above, or with a particular section			✓

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
of labeling. CDRH should also consider posting on its public 510(k) database the version of the labeling cleared with each submission as "preliminary labeling," in order to provide this information even before the Center has received and screened final labeling.			
The 510(k) Working Group recommends that CDRH develop guidance and regulations regarding appropriate documentation of transfers of 510(k) ownership. The Center should update its 510(k) database in a timely manner when a transfer of ownership occurs.	✓		
The 510(k) Working Group recommends that CDRH continue to take steps to enhance recruitment, retention, training, and professional development of review staff, including providing opportunities for staff to stay abreast of recent scientific developments and new technologies. This should include increased engagement with outside experts, as discussed further in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making (described further in Section 2, below).	✓		
The 510(k) Working Group further recommends that CDRH consider establishing a Center Science Council comprised of experienced reviewers and managers and under the direction of the Deputy Center Director for Science. The Science Council should serve as a cross-cutting oversight body that can facilitate knowledge-sharing across review branches, divisions, and offices, consistent with CDRH's other ongoing efforts to improve internal communication and integration. The Science Council's role in improving the consistency of Center decisions is discussed in greater detail in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making.		✓	
The 510(k) Working Group recommends that CDRH develop a process for regularly evaluating the list of device types eligible for third-party review and adding or removing device types as appropriate based on available information. The Center should consider, for example, limiting eligibility to those device types for which device-specific guidance exists, or making ineligible selected device types with a history of design-related problems.			✓
The 510(k) Working Group further recommends CDRH enhance its third-party reviewer training program and consider options for sharing more information about previous decisions with third-party reviewers, in order to assure greater consistency between in-house and third-party reviews.	✓		
The 510(k) Working Group recommends that CDRH develop metrics to continuously assess the quality, consistency, and effectiveness of the 510(k) program, and also to measure the effect of any actions taken to improve the program. As part of this effort, the Center should consider how to make optimal use of existing internal data sources to help evaluate 510(k) program performance.	✓		
The 510(k) Working Group further recommends that CDRH periodically audit 510(k) review decisions to assess adequacy, accuracy, and consistency. The ongoing implementation of iReview (described in Section 5.3.2 of this report), as part of the Center's FY 2010 Strategic Priorities, could assist with this effort by allowing CDRH to more efficiently search and analyze completed reviews. These audits should be overseen by the new Center Science		✓ Define objective of audit and authority of Council; do not support authority to reverse	

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
Council, described above, which would also oversee the communication of lessons learned to review staff, as well as potential follow-up action.		decisions.	
SCIENCE REPORT			
The Task Force recommends that CDRH revise its 2002 "least burdensome" guidance to clarify the Center's interpretation of the "least burdensome" provisions of the Federal Food, Drug, and Cosmetic Act (21 USC § 360c(a)(3)(D)(ii) and 21 USC § 360c(i)(1)(D)). CDRH should clearly and consistently communicate that, while the "least burdensome provisions" are, appropriately, meant to eliminate unjustified burdens on industry, such as limiting premarket information requests to those that are necessary to demonstrate reasonable assurance of safety and effectiveness or substantial equivalence, they are not intended to excuse industry from pertinent regulatory obligations nor to lower the Agency's expectations with respect to what is necessary to demonstrate that a device meets the relevant statutory standard.		✓ No need to revise guidance; train industry and FDA on existing guidance.	
The Task Force recommends that CDRH continue its ongoing efforts to improve the quality of the design and performance of clinical trials used to support premarket approval applications (PMAs), in part by developing guidance on the design of clinical trials that support PMAs and establishing an internal team of clinical trial experts who can provide support and advice to other CDRH staff, as well as to prospective investigational device exemption (IDE) applicants as they design their clinical trials. The Center should work to assure that this team is comprised of individuals with optimal expertise to address the various aspects of clinical trial design, such as expertise in biostatistics or particular medical specialty areas. The team would be a subset of the Center Science Council discussed in Section 4.2.1 of this report, and, as such, it may also serve in the capacity of a review board when there are differences of opinion about appropriate clinical trial design and help assure proper application of the least burdensome principle. CDRH should also continue to engage in the development of domestic and international consensus standards, which, when recognized by FDA, could help establish basic guidelines for clinical trial design, performance, and reporting. In addition, CDRH should consider expanding its ongoing efforts related to clinical trials that support PMAs, to include clinical trials that support 510(k)s.		✓ Include all stakeholders in development of guidance.	
The Task Force recommends that CDRH work to better characterize the root causes of existing challenges and trends in IDE decision making, including evaluating the quality of its pre-submission interactions with industry and taking steps to enhance these interactions as necessary. For example, the Center should assess whether there are particular types of IDEs that tend to be associated with specific challenges, and identify ways to mitigate those challenges. As part of this process, CDRH should consider developing guidance on pre-submission interactions between industry and Center staff to supplement available guidance on pre-IDE meetings.	✓		

CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
The Task Force recommends that CDRH consider creating a standardized mechanism whereby review Offices could rapidly assemble an ad hoc team of experienced review staff from multiple divisions to temporarily assist with time-critical work in a particular product area, as needed, in order to accommodate unexpected surges in workload. This would need to be done in such a way that ad hoc teams would only assist with work that does not require specialized subject matter expertise beyond what the team members possess. The Task Force recognizes that such an approach is only a stop-gap solution to current workload challenges, and that additional staff will be necessary to better accommodate high workloads in the long term. The Center's staffing needs are discussed further below.		✓ Ensure routine work is not adversely affected; ensure oversight of team work.	
The Task Force recommends that CDRH assess and better characterize the major sources of challenge for Center staff in reviewing IDEs within the mandatory 30-day timeframe, and work to develop ways to mitigate identified challenges under the Center's existing authorities.		✓ Do not expend valuable resources; develop guidance for pre-IDE meetings.	
The Task Force recommends that CDRH continue ongoing efforts to develop better data sources, methods, and tools for collecting and analyzing meaningful postmarket information, consistent with the Center's FY 2010 Strategic Priorities. In addition, the Center should conduct a data gap analysis and a survey of existing U.S. and international data sources that may address these gaps. These efforts should be in sync with and leverage larger national efforts. As CDRH continues its efforts to develop better data sources, methods, and tools, it should invite industry and other external constituencies to collaborate in their development and to voluntarily provide data about marketed devices that would supplement the Center's current knowledge.		✓ Continued validation of data owners, research contractors, study methods, and data sets.	
The Task Force recommends that CDRH conduct an assessment of its staffing needs to accomplish its mission-critical functions. The Center should also work to determine what staff it will need to accommodate the anticipated scientific challenges of the future. CDRH should also take steps to enhance employee training and professional development to assure that current staff can perform their work at an optimal level. As part of this process, the Center should consider making greater use of professional development opportunities such as site visits or other means of engagement with outside experts in a variety of areas, including clinical care, as described below. This recommendation complements the Center's ongoing efforts under its FY 2010 Strategic Priorities to enhance the recruitment, retention, and development of high-quality employees.	✓		
The Task Force recommends that CDRH continue the integration and knowledge management efforts that are currently underway as part of the Center's FY 2010 Strategic Priorities. As part of these efforts, the Task Force recommends that CDRH develop more effective mechanisms for cataloguing the Center's internal expertise, assess the effectiveness of the inter-Office/Center consult process, and enhance the infrastructure and tools used to provide meaningful, up-to-date information about a given device or group of	✓		

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
devices to Center staff in a readily comprehensible format, to efficiently and effectively support their day-to-day work.			
The Task Force recommends that CDRH, consistent with the Center's FY 2010 Strategic Priorities, develop a web-based network of external experts, using social media technology, in order to appropriately and efficiently leverage external expertise that can help Center staff better understand novel technologies, address scientific questions, and enhance the Center's scientific capabilities.		✓ Explain use of social media technology; ensure confidentiality of information; define expert selection process.	
The Task Force recommends that CDRH assess best-practices for staff engagement with external experts and develop standard business processes for the appropriate use of external experts to assure consistency and address issues of potential bias. As part of this process, the Center should explore mechanisms, such as site visits, through which staff can meaningfully engage with and learn from experts in a variety of relevant areas, including clinical care. In addition to supporting interaction at the employee level, the Center should also work to establish enduring collaborative relationships with other science-led organizations.	✓		
The Task Force recommends that CDRH develop and implement a business process for responding to new scientific information in alignment with a conceptual framework comprised of four basic steps: (1) detection of new scientific information; (2) escalation of that information for broader discussion with others; (3) collaborative deliberation about how to respond; and (4) action commensurate to the circumstance — including, potentially, deciding to take no immediate action. As it puts this approach into practice, CDRH should consider adopting several key principles. First, the process should allow for a range of individuals to participate in the deliberation phase, including managers and employees, to help take into consideration potentially cross-cutting issues and assure consistency in responding to new scientific information. To support this principle, CDRH should establish a Center Science Council, comprised of experienced employees and managers and under the direction of the Deputy Center Director for Science, to provide oversight and help assure consistency across the Center. Second, the process should be streamlined to allow for new information to be raised and addressed in a timely manner. Third, the process should include a mechanism for capturing in a structured manner the rationale for taking a particular course of action, so that it can be articulated clearly to staff and external constituencies and incorporated into the Center's institutional knowledge base. Fourth, the process should be designed to allow for prioritization of issues. The Center should also develop metrics to determine whether or not the new process is effective.		✓ Include industry in steps 3 and 4	
The Task Force recommends that CDRH enhance its data sources, methods, and capabilities to support evidence synthesis and quantitative decision making as a long-term goal.	✓		

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
The Task Force recommends that CDRH continue its ongoing efforts to streamline its processes for developing guidance documents and regulation, consistent with the Center's FY 2010 Strategic Priorities. For example, CDRH should explore greater use of the "Level 1 – Immediately in Effect" option for guidance documents intended to address a public health concern or lessen the burden on industry. CDRH should also encourage industry and other constituencies to submit proposed guidance documents, which could help Center staff develop Agency guidance more quickly.		✓ Ensure use of Level 1 is limited to public health concerns	
The Task Force recommends that CDRH establish as a standard practice sending open "Notice to Industry" letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations on the basis of new scientific information. CDRH should adopt a uniform template and terminology for such letters, including clear and consistent language to indicate that the Center has changed its regulatory expectations, the general nature of the change, and the rationale for the change. Currently, manufacturers typically learn of such changes through individual engagement with the Agency, often not until after they have prepared a premarket submission. The aim of issuing a "Notice to Industry" letter would be to provide greater clarity to manufacturers, in a timelier manner, about the Center's evolving expectations with respect to a particular group of devices. Because a change in regulatory expectations would represent a change in policy, a "Notice to Industry" letter would likely be considered guidance, although it would typically be issued relatively quickly and would generally not contain the level of detail traditionally found in other guidance documents. In the interest of rapidly communicating the Center's current regulatory expectations to industry, CDRH would generally issue "Notice to Industry" letters, if such letters constitute guidance, as "Level 1 – Immediately in Effect" guidance documents, and would open a public docket in conjunction with their issuance through a notice of availability in the Federal Register. To expedite the issuance of "Notice to Industry" letters, CDRH should develop standardized templates for these letters and, as necessary, their accompanying Federal Register notices. In addition, when appropriate, CDRH should follow "Notice to Industry" letters as soon as possible with new or modified guidance explaining the Center's new regulatory expectations in greater detail and revising the guidance where necessary in response to comments received, so that external constituencies have a fuller understanding of the Center's current thinking. CDRH should also consider creating a webpage for identifying and explaining new information that has altered the Center's regulatory expectations, so that, across all CDRH-regulated products, external constituencies can better understand the rationale for changes in the Center's requirements.		✓ Clearly define circumstances for use; establish implementation timeframes; make NIT public, not limited to current manufacturers	
The Task Force recommends that CDRH take steps to improve medical device labeling,			✓
and to develop an online labeling repository to allow the public to easily access this information. The possibility of posting up-to-date labeling for 510(k) devices online is			✓

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
described in greater detail in the preliminary report of the 510(k) Working Group (described further in Section 3, below).			
The Task Force recommends that CDRH develop and make public a Standard Operating Procedure (SOP) that describes the process the Center will take to determine the appropriate response to new scientific information, based on the conceptual framework outlined above. The SOP should include the expectation that when a decision is made to take a particular course of action, including a change in evidentiary expectations, the action and its basis should be communicated clearly and promptly to all affected parties. If it is not possible to provide complete detail about the basis for an action due to confidentiality concerns, Center staff should share as full an explanation as is allowable and state why a more complete explanation is not permissible. In addition, Center leadership should take steps to make sure that all employees have an accurate understanding of what information they are permitted to discuss with manufacturers, so that information that would help clarify the basis for a particular action is not needlessly withheld.		✓ Involve all stakeholders in developing the procedure	
The Task Force recommends that CDRH continue its ongoing efforts to make more meaningful and up-to-date information about its regulated products available and accessible to the public through the CDRH Transparency Website, consistent with the Center's FY 2010 Strategic Priorities and the work of the FDA Transparency Task Force. In addition to the pre- and postmarket information that is already available on CDRH Transparency Website, the Center should move to release summaries of premarket review decisions it does not currently make public (e.g., ODE 510(k) review summaries) and make public the results of post-approval and Section 522 studies that the Center may legally disclose. Making such information readily available to the public will provide CDRH's external constituencies with greater insight into the data that guide the Center's decisions and evolving thinking.		✓ Do not post decisions of devices that were not cleared.	

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Specific Comments

1. A Rational, Well-Defined, and Consistently Interpreted Review Standard

RECOMMENDATION: *CDRH should clarify the meaning of "substantial equivalence" through guidance and training for reviewers, managers, and industry.*

"Same Intended Use"

Lack of a Clear Distinction between Terms

Recommendation: *The 510(k) Working Group recommends that CDRH revise existing guidance to consolidate the concepts of "indication for use" and "intended use" into a single term, "intended use," in order to reduce inconsistencies in their interpretation and application. Several public comments expressed concern that, if these two terms were combined, any proposed change in a device's label indications could be considered a change in "intended use." The Working Group recognizes the importance of providing submitters with the flexibility to propose certain changes to their labeling, without such a change necessarily constituting a new "intended use." Therefore it recommends that CDRH carefully consider what characteristics should be included under the term "intended use," so that modifications that are currently considered to be only changes in "indications for use" and that CDRH determines do not constitute a new "intended use," are not in the future necessarily construed as changes in "intended use" merely because of a change in semantics. Any change in terminology would be intended to provide greater clarity and simplicity, not necessarily to make the concept of "intended use" more restrictive. The Center should also carefully consider what it should call the existing "Indications for Use" statement in device labeling and the "Indications for Use" form currently required for all 510(k)s, in order to avoid confusion in terminology but still maintain an appropriate level of flexibility for submitters.*

AdvaMed does not support the consolidation of "intended use" and "indications for use" into a single term, and maintains that there is value in preserving these terms as separate concepts because the terms are not synonymous. It is critical that the two concepts remain distinct and separate, as they clearly serve different purposes. "Intended use" broadly describes the use of a generic type of device (i.e., what the device does) while "indications for use" more specifically describes the device's clinical uses and patient population(s). Combining the two terms may constrain the meaning of intended use, remove the flexibility that is currently afforded to the Agency in determining what new uses should be regulated within the confines of Section 510(k), and unnecessarily narrow the meaning of substantial equivalence. Indeed, combining the terms eliminates the distinction between "general" and "specific" uses that FDA has relied upon in determining whether the addition of a specific indication for use may trigger the need for additional data, including clinical data, versus the need for a PMA or a *de novo* classification.[2]

[2] *See* FDA Guidance for Industry: General/Specific Intended Use (1998). Available at: http://www.fda.gov/MedicalDeviceRegulationandGuidance/GuidanceDocuments/ucm073944.htm.

FDA has recognized that the addition of a specific indication may or may not alter a device's intended use, depending on a multitude of factors. Furthermore, removing the "Indications for Use" terminology from its tool box will result in confusion among patients and health care professionals who rely on the indications for use appearing in product labeling consistent with other FDA-regulated products. If, however, FDA determines that the intended use is altered, it will issue an NSE determination. FDA needs to retain the flexibility of considering those factors. From a patient perspective, we are concerned that patient access to new devices would be delayed because of a potential increase in Not Substantially Equivalent (NSE) determinations resulting from a combination of these two terms.

AdvaMed believes that the specific differences between the terms, "intended use" and "indications for use," can be clarified by developing definitions of each concept within the context of substantial equivalence. The Code of Federal Regulations (21 C.F.R. § 801.4) provides a definition of intended use in the context of postmarket behavior related to the need for adequate directions for use as described in 21 C.F.R. § 801.5, and indications for use is defined in the PMA regulations (21 C.F.R. § 814.20). Neither is defined for use in the context of substantial equivalence. With that in mind, AdvaMed recommends adding definitions in 21 C.F.R. Part 807 that clarify the use of these terms in the premarket notification context.

AdvaMed recommends amending 21 C.F.R. Part 807 to include a discussion of intended use and indications for use. We suggest that the following section be added to Part 807:

> **New Section § 807.80 *Meaning of Intended Use and Indications for Use***
> **The words *intended use* in § 807.100(b)(1) refer to a regulatory concept that determines the boundaries of use for a generic type of device. *Intended use* is constructed to encompass the appropriate breadth of use for which the regulatory controls for the generic device type continue to provide reasonable assurance of safety and effectiveness. The words *intended use* refer to the objective intent for the device function by the persons legally responsible for the proposed labeling of the device that is the subject of the premarket notification submission. *Intended use* describes what the device is intended to provide to the user and patient and for what purpose. Objective intent may be inferred from such persons' written or oral expressions, or the design of the device, however, for the purpose of determining substantial equivalence, the objective intent must be determined from the proposed labeling.[3] *"Indications for use"* provides a detailed, specific description of the specific target population(s) for the intended use that generally describes device function, and includes the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, and/or a description of the general or specific patient populations or anatomies for which the device is intended, as appropriate.**

[3] This aspect of our proposed definition of intended use derives from Section 513(i)(1)(E)(1) of the Act, which states that "[a]ny determination by the Secretary of the intended use of a device [for the purpose of determining substantial equivalence] shall be based upon the proposed labeling submitted in a report for the device under Section 510(k)."

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AdvaMed supports the development of guidance documents that *clarify* the meanings of "intended use" and "indications for use," rather than revising existing guidance to consolidate these terms, as recommended by the 510(k) Working Group. Examples distinguishing intended use from indications for use that could be provided in future guidance documents include:

- The *intended use* of an electrosurgical cutting and coagulation device is to remove tissue and control bleeding by use of high-frequency electrical current (21 C.F.R. § 878.4400). Electrosurgical cutting and coagulation devices, however, may be specifically designed to accommodate different anatomies. They may have *indications for use* in thoracic, gynecologic, ENT, or other procedures, as illustrated by the 31 product classification codes for electrosurgical instruments.

- The *intended use* of an infusion pump is to deliver fluid to a patient in a controlled manner (21 C.F.R. § 880.5725). External infusion pumps may have any of the following *indications for use*:
    - general administration of drug solutions vs. blood vs. insulin.
    - intravenous, epidural, subcutaneous, subarachnoid, etc.
    - patient-controlled analgesia
    - hospital versus home use

- The *intended use* of a gas analyzer is to provide a means of monitoring gas concentration and to alert clinical personnel when limits fall outside of a pre-specified range (there are over 15 classification regulations for gas analyzers). The indications for use of a gas analyzer could be for an anesthetic agent, or oxygen, carbon dioxide, or nitrous oxide.

AdvaMed notes that not all devices subject to 510(k) have both an intended use and an indication for use (e.g., a syringe delivers whatever liquid it contains, what it delivers is not specified, and there is no specific patient population). Also with respect to intended use, AdvaMed recommends that FDA take into consideration that intended use for *in vitro* diagnostic devices may include what is being measured, and for what purpose. However, the intended use should not extend to an IVD's particular performance characteristics (e.g., accuracy, ranges, or cut-off values).

AdvaMed also recommends that FDA continue the practice of attaching an "Indications for Use" form to all substantially equivalent (SE) letters. The Indications for Use form provides a transparent means through which all stakeholders are able to clearly identify the indications for use that have been accepted by FDA. Because of the significant impact of any modifications to the definitions of intended use and indications for use, we believe it is necessary for the Agency to provide notice and an opportunity for public comment.

AdvaMed supports the Working Group's recommendation that the Indications for Use statement (if any) be included in the *labeling* but that it should not be provided directly on the package *label*. Further, some packages are not sized to contain this information and there is an environmental issue associated with increased packaging. This requirement would necessitate

the amendment of 21 C.F.R. Part 801, requiring notice and comment. Users are provided with the product labeling, which already contains the Indications for Use.

Insufficient Guidance for 510(k) Staff and Industry

Recommendation: *The 510(k) Working Group recommends that CDRH develop or revise existing guidance to clearly identify the characteristics that should be included in the concept of "intended use."*

AdvaMed supports the revision of existing guidance to clarify the terms "intended use" and "indications for use," but does not support the recommendation to consolidate these terms.

Recommendation: *The 510(k) Working Group further recommends that CDRH provide training for reviewers and managers on how to determine "intended use." Such training should clarify the elements of a device application that should be considered when determining the "intended use," e.g., product labeling, device design (explicit or implied), literature, and existing preclinical or clinical data. Training on "intended use" should also be provided to industry.*

If FDA adopts AdvaMed's recommended definition of "intended use" and "indications for use," then FDA should conduct training of review staff on to determine these terms.

Off-Label Use

Recommendation: *The 510(k) Working Group recommends that CDRH explore the possibility of pursuing a statutory amendment to section 513(i)(1)(E) of the Federal, Food , Drug and Cosmetic Act ... that would provide the agency with the express authority to consider an off-label use, in certain limited circumstances, when determining the "intended use" of a device under review through the 510(k) process.*

AdvaMed does not support this recommendation. AdvaMed does not agree with granting additional authority to FDA when the Agency believes that a device's primary intended use is an off-label use that is not reflected in the proposed labeling. FDA currently has statutory authority to act on off-label use that could cause harm by requiring a statement in the product labeling.

Congress has previously addressed this issue. In the Food and Drug Administration Modernization Act of 1997 (FDAMA), Congress clearly defined the approach the Agency must take when identifying concerns regarding potential off-label use of devices undergoing 510(k) review. This approach, codified at Section 513(i)(1)(E)(i) of the Act,[4] provides that the

[4] Section 513(i)(1)(E)(i) of the Act provides that "[a]ny determination by the Secretary of the intended use of a device shall be based upon the proposed labeling submitted in a report for the device under Section 510(k). However, when determining that a device can be found substantially equivalent to a legally marketed device, the director of the organizational unit responsible for regulating devices (in this subparagraph referred to as the "Director") may require a statement in labeling that provides appropriate information regarding a use of the device not identified in the proposed labeling if, after providing an

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Agency's determination of intended use "shall be based upon the proposed labeling," but that the Agency may address concerns about potential off-label use through requiring a statement in the labeling, after consulting with the applicant and if the following criteria are met: if there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device, and if such use could cause harm.

We do not believe that there is a need for any further restrictions on 510(k) clearance related to potential off-label use. A properly administered 510(k) program ensures that devices receiving FDA clearance are suitable for the intended use and indications for use in the proposed labeling for which they are being cleared. The determination of substantial equivalence should not take into account potential off-label uses, and clearance should not be withheld for the requested use pending submission of data for a suspected off-label use that the sponsor has not requested. Instead, the statute directs CDRH to address those concerns by requiring statements in the labeling, including limitations within the intended use statement -- without otherwise affecting a substantial equivalence determination. This Congressionally-mandated path provides a more flexible path for CDRH to follow while protecting public health, and is less onerous for both the Agency and industry.

AdvaMed does not support the expansion of FDA's authority to consider an off-label use as the primary intended use. This expanded authority would place reviewers in the untenable position of second guessing the sponsor's intentions and would be disruptive to the 510(k) program. Further, a 510(k) could automatically receive an NSE determination if the sponsor has not provided data on what FDA presumed to be the primary use, thereby leading to an NSE decision for the legitimate 510(k) use requested by the sponsor.

Companies with the intent to market a device for a legitimate intended use should not be prevented from obtaining 510(k) clearance because other product uses may exist. In fact, in a unanimous decision, the United States Supreme Court has acknowledged the importance of off-label use in *Buckman v. Plaintiffs' Legal Committee*, No. 98-1768, stating that, "Off-label" usage of medical devices (use of a device for some other purpose than that for which it has been approved by the FDA) is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine." Further, the possibility of a CDRH decision to require a company to support an additional intended use may result in the company's decision not to pursue commercial development of a new and potentially useful device or diagnostic, further stifling innovation. Additionally, such a requirement could represent an undue hardship to a smaller company that does not have the economic means to pursue a use it did not intend.

As noted above, where CDRH has concerns that there is a reasonable likelihood that the device will be used outside of the proposed labeling and when that use potentially could cause harm, it

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opportunity for consultation with the person who submitted such report, the Director determines and states in writing "(I) that there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device; and (II) that such use could cause harm."

now issues an SE with limitations decision and requires manufacturers to include adequate warnings against such use in the labeling. Likewise, in the postmarket period, the Agency has the ability to deal with manufacturers that engage in off-label promotional activities. Specifically, 21 C.F.R. 801.4 provides the Agency with considerable discretion in identifying off-label uses and company activities geared toward off-label promotion. When these situations arise, FDA can take many actions to stop off-label promotion and to encourage compliance with applicable requirements.

When substantial off-label use is discovered in the postmarket period and the company has not illegally promoted such use, FDA should encourage companies to seek clearance for the off-label use and to develop adequate directions for use for these new clinical applications, or to add or maintain a specific limitation in labeling for the device. In instances where the company wishes to include the off-label use(s), FDA should work with the company to identify the type of data required to support an expanded use.

Different Questions of Safety and Effectiveness

Inconsistent Terminology

Recommendation: *The 510(k) Working Group recommends that CDRH reconcile the language in its 510(k) flowchart (shown on page 27 of this report) with the language provided in section 513(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360c(i) regarding "different technological characteristics" and "different questions of safety and efficacy."*

AdvaMed does not support the 510(k) Working Group s recommendation that the language in FDA s 510(k) flowchart and the statutory language in 513(i) of the Act be reconciled. As reflected in Blue Book memorandum K86-3, the Agency has interpreted different questions to be new types of questions. AdvaMed believes that the current wording in the flowchart fits within the intent of the statute. It is a long-standing and well-established interpretation that has worked well for many years. By inserting the words new types, it is our understanding that the Agency was indicating that different questions can be grouped in a manner that provides FDA appropriate discretion in deciding what scientific questions justify making a new device NSE on this basis. As a result, any modification of this well-established approach is a new interpretation, which requires notice and comment.

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Insufficient Guidance for 510(k) Staff and Industry

Recommendation: *The 510(k) Working Group recommends that CDRH revise existing guidance to provide clear criteria for identifying "different questions of safety and effectiveness" and to identify a core list of technological changes that generally raise such questions (e.g., a change in energy source, a different fundamental scientific technology).*

AdvaMed supports the Working Group's recommendation for clear guidance, subject to notice and comment, focused on the use of risk assessments in identifying potential "new types" of safety and effectiveness questions. The use of flowcharts differentiating elements for consideration would further clarify the process.

Recommendation: *The 510(k) Working Group further recommends that CDRH develop and provide training for reviewers and managers on how to determine whether a 510(k) raises "different questions of safety and effectiveness." Training on "different technological characteristics" and "different questions of safety and effectiveness" should also be provided to industry.*

AdvaMed supports the Working Group's recommendation to train reviewers and managers on "new types of safety and effectiveness questions." Training should be provided to reviewers, managers, and industry so that all understand that when questions are raised by a new technology, and they can be answered by established and/or recognized standards, or established, recognized, or validated test methods, then an NSE determination is not the automatic result. AdvaMed further recommends that CDRH focus on clarifying which questions of safety and efficacy are "different," or "new types," rather than on the underlying device technology and its characteristics.

AdvaMed believes that a question of safety and effectiveness is not "different" if the question can be answered through established, well recognized, or validated test methods. Advances in materials science provide examples of how specific scientific questions can be approached in the context of SE decision-making. In the medical device industry, manufacturers constantly search for new materials. As new materials are identified, questions often arise regarding their suitability for a particular use. While the use of a new material in a device may raise questions, historically FDA has considered the question to be of the same "type" that previous materials have raised and, therefore, have not generally viewed changes in materials as a justification for a NSE decision. As an alternative to considering which questions are of the same type and which are not, focusing on what testing is required to address the question, and whether the testing involves well established and recognized methods removes much of the subjectivity. In the context of the latest materials science, questions regarding a new material's ability to meet the demands of a particular use environment can usually be addressed through bench and animal testing.

Recommendation: *CDRH should explore the development of guidance and regulation to provide greater assurance that any comparison of a new device to a predicate is valid and well-reasoned.*

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Concerns about Predicate Quality

Recommendation: *The 510(k) Working Group recommends that CDRH consider developing guidance on when a device should no longer be available for use as a predicate because of safety and/or effectiveness concerns. It is expected that such a finding would be an uncommon occurrence. Any factors set forth in guidance regarding when a device should no longer be used as a predicate should be well-reasoned, well-supported, and established with input from a range of stakeholders, and unintended consequences should be carefully considered.*

AdvaMed does not support the Working Group's recommendation that CDRH develop guidance on when a device should no longer be available for use as a predicate. AdvaMed believes that statutory change is required to disqualify a legally marketed device from being available for use as a predicate because of purported safety or effectiveness concerns, and cannot be accomplished by guidance. AdvaMed does not believe, however, that it is necessary to promulgate new legislation, as FDA already has the authority to remove violative devices from the market. Under Section 513(i)(2) of the Act, those devices that have been removed from the market by FDA or have been determined adulterated or misbranded by a judicial order are disqualified from being predicate devices. Simply put, guidance documents cannot create requirements and cannot supersede statutory law. CDRH's current statutory remedy to a device that it believes is unsafe or ineffective is to bring an enforcement action to remove the device from the market (i.e., the Agency may ban the device). In addition, if the controls for assuring safety or effectiveness are inadequate, CDRH can develop special controls or reclassify the device. Using guidance to shortcut the statute is without legal basis and unacceptable.

The 510(k) Working Group's concerns appear not to be relevant to 510(k)s reviewed by the Office of *In Vitro* Diagnostics (OIVD). OIVD informs companies of the product or technology to which the 510(k) device must be compared (gold standard: e.g., bacteriological media/culture for many infectious diseases), thereby reducing the risk of safety and effectiveness concerns with the predicate device(s).

AdvaMed further notes that there are a number of older devices that remain relevant to current standards of care or remain popular because they represent a more affordable option than the latest technology. There also may be attributes of older predicate devices that are relevant to the newer technologies. AdvaMed also notes that devices evolve as new technological advances are made, and are not expected to be identical to the older predicate devices. For example, if FDA has concerns about the safety and effectiveness of a legally marketed device, those concerns may not apply to the 510(k) device because of technological improvements, and FDA has full statutory authority to require evidence that the technological characteristics of the new device do not raise new/different safety and effectiveness concerns. Finally, AdvaMed notes that not all devices are removed from the market because of reasons that would disallow their use as a predicate (i.e., safety and effectiveness concerns). For example, companies will discontinue a product line for business reasons unrelated to safety and effectiveness.

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Rescission Authority

Recommendation: *The 510(k) Working Group recommends that CDRH consider issuing a regulation to define the scope, grounds, and appropriate procedures, including notice and an opportunity for a hearing, for the exercise of its authority to fully or partially rescind a 510(k) clearance. As part of this process, the Center should also consider whether additional authority is needed.*

AdvaMed does not support the issuance of a regulation to exercise rescission authority nor does AdvaMed support expansion of rescission authority. AdvaMed believes that, absent the commission of an act of fraud in establishing the substantial equivalence of a device, rescission would not be justified and should not be allowed, because of the "domino effect" it could have. If FDA had the authority to rescind a 510(k) for reasons other than fraud, the legal marketing status of each device that had subsequently relied on the rescinded device as a predicate would be jeopardized (i.e., the device would be misbranded), even if the concerns that prompted the rescission of the predicate device do not apply to the subsequent devices. Expanding FDA's 510(k) rescission authority to include rescission based on safety or effectiveness concerns is not only unnecessary, it also would cause more harm than good for several reasons. The 510(k) clearance system is a classification process and is based on predicates. Once a device is cleared and FDA has made the decision that its design and intended use are substantially equivalent to a predicate device, FDA should not rescind that decision because, for example, a device is manufactured under poor conditions that impair its safety or effectiveness or because a manufacturer has changed the device's design. If a predicate, key to a line of subsequent devices, is rescinded, it could result in each and every device that cites the rescinded device being rescinded as well, even when those devices do not share whatever defect occurred in the rescinded device, with a potentially significant impact to public health. As noted above, FDA currently has the tools to isolate a device that violates any part of the Act, is determined not to be substantially equivalent to a predicate, or is not safe and effective to protect the public health without creating unreasonable jeopardy for innocent parties.

The Act provides FDA with numerous tools to remove violative devices from the market and should not accomplish it in a way that may broadly limit access to safe and effective medical devices, thus undermining the public health. If a device is considered unsafe because it is manufactured under noncompliant GMPs, is manufactured incorrectly, or the manufacturer has changed the design without meeting the appropriate 510(k) premarket requirements, then that device should be appropriately dispositioned per FDA's current postmarket authorities provided in the Act. These authorities include reclassification, recall, warning letters, and other enforcement actions. In addition, the Act already provides for the banning of a medical device in situations of substantial deception or unreasonable and substantial risk of illness or injury.[5] Banned medical devices can no longer be legally marketed and can therefore not be cited as a predicate device. FDA also has the authority to issue an order for mandatory device recall[6] or to

[5] See Section 516 of the Act

[6] See Section 518 of the Act

reclassify a device.[7] FDA also may, when necessary, obtain court orders for product seizure. These conditions can be remedied, however, and should not be used as grounds for revoking the original 510(k) decision, because the currently available statutory tools enable the Agency to protect the public health and also maintain the integrity of the classification system.

AdvaMed agrees that FDA can nullify a substantial equivalence determination, if the 510(k) submitter procured the determination through fraud, or if the Agency made an inadvertent administrative mistake or error and corrected it prior to the order becoming final. Rescinding one 510(k) clearance could potentially reclassify a group of devices, and FDA does not need to take such action in order to protect the public health. The Act provides the Agency with numerous efficient means to remove unsafe or violative devices from the market. Moreover, the Act authorizes FDA to reclassify devices based on new information, including reassessment of past information in the administrative record.

In summary, FDA does not have express or implied statutory authority to rescind 510(k) classification determinations, nor are there compelling policy grounds to do so. The Working Group indicated that rescission would be seldom used in response to particular circumstances; we believe the law now provides adequate remedies for any such circumstance and fully provides adequate protection of the public health if the Agency is willing to use the remedies Congress gave it to ensure safe and effective devices. Outside of the limiting circumstances described above, undermining the predicate status of a device through rescission would not advance the public health and would undermine the entire classification system set forth in the Act.

Please see the detailed legal analysis of FDA's proposed expanded rescission authority provided in Attachment B.

Use of "Split Predicates" and "Multiple Predicates"

Recommendation: *The 510(k) Working Group recommends that CDRH develop guidance on the appropriate use of more than one predicate, explaining when "multiple predicates" may be used. The Center should also explore the possibility of explicitly disallowing the use of "split predicates." In addition, CDRH should update its existing bundling guidance to clarify the distinction between multi-parameter or multiplex devices (described in Section 5.1.2.3 of this report) and bundled submissions (described in Section 4.3.4.2).*

AdvaMed is opposed to disallowing the use of split predicates and supports the use of multiple predicates. The current bundling guidance works well for bundled submissions, and the only revision necessary is to clarify the distinction between multi-parameter or multiplex devices. AdvaMed supports updating CDRH's existing bundling guidance only to clarify the distinction between multi-parameter or multiplex devices. AdvaMed believes that the use of multiple

[7] See Section 513(e) of the Act.

predicates, i.e., using more than one predicate where each predicate individually supports substantial equivalence, is and should continue to be permissible under the 510(k) process. A 510(k) submission utilizing multiple predicates must still provide a clear demonstration of safety and effectiveness. Further, disallowing the use of "split predicates" and/or arbitrarily disallowing the use of more than five predicates for a given device under 510(k) review could result in an unnecessary burden on the PMA and *de novo* submission programs for both CDRH and industry, resulting in delayed or no patient access to new devices. The bases for our positions are detailed below.

"Split" Predicates

In its August report, FDA defined "split" predicates as taking the intended use from one device and the technology from another device and putting those two together to try to reach a substantial equivalence determination. Per statute, the new device must always have the same intended use as the predicate device. Different technology is permissible provided that the different technology does not raise new or different types of questions. First and foremost, and as noted above, AdvaMed opposes disallowing the use of "split predicates." Such an action will stifle innovation and evolutionary change in device design, which the 510(k) program was designed to encourage.

The use of split predicates is a reasonable approach to showing substantial equivalence. We believe the use of a split predicate is vital to innovation and to the public health goals of the 510(k) program because many devices are modular in nature (i.e., they are made up of a combination of components). AdvaMed believes that FDA should allow the submission of 510(k)s in accordance with actual product configuration, enabling the use of split predicates where appropriate.

In cases where split predicates are used, the 510(k) sponsor should be required to provide risk-based justification for using split predicates for their particular device. This risk-based approach is consistent with the concepts behind "multiple predicates" and the dual goal of CDRH to protect public health while encouraging device innovation. Guidance documents should include CDRH's current thinking on acceptable risk-based justifications to encourage high-quality 510(k) filings. Further, reviewers should be trained on the use of split predicates.

Split predicates add to the dataset for FDA to consider in a useful manner. While there is often a "core" predicate based on intended use or mode of action, it may not seem comparable owing to a different feature such as power source, materials, or technology. Being able to demonstrate to FDA that there is marketing experience to be drawn upon for this different feature allows FDA to consider all of the available information and make an informed judgment as to the level of risk introduced by the new product.

Please note that the IVD practice of providing performance data against both a "gold standard" and a predicate is not the same as the use of split (or multiple) predicates. The data from the reference method, or gold standard, are meant to provide additional information on the IVD's

accuracy as compared to a recognized method, not to demonstrate substantial equivalence. The predicate is used to demonstrate substantial equivalence.

Multiple Predicates

Since 1986, the Agency has recognized the concept of multiple predicates in cases where new devices and multiple predicates have compatible intended uses. Specifically, in a 1986 guidance,[8] FDA stated that a new device made up of a combination of devices of different types and classifications could be substantially equivalent to multiple predicates; however, the classification of the new device would be that of the highest classification of the predicates relied upon to show substantial equivalence. By extension, multiple predicates for new devices within the same generic type are permissible and consistent with FDA's longstanding interpretation of its premarket notification classification provisions.

AdvaMed supports the development of guidance for use of multiple predicates, but does not support any guidance that arbitrarily restricts the number of predicate devices that can be used. FDA should expect a 510(k) submission to provide a clear demonstration of safety and effectiveness, and that the aggregate of the components does not create new or different questions of safety or effectiveness. To curtail such an approach would, in some cases, require multiple, step-wise 510(k)s that would significantly delay introduction of more practical technology and would burden the review system with unnecessary 510(k)s.

Even if FDA were to eliminate the ability for 510(k) submitters to rely on multiple predicates, new devices that incorporate features of more than one legally marketed Class I or Class II device could still be classified into either class under the *de novo* process and could then serve as predicates for subsequent devices. The *de novo* classified device could then serve as a predicate for each of the predicates that would have been cited if a multiple predicate approach had been allowed. In other words, changing the Agency's historical use of multiple predicates elevates form over substance and fails to advance the public health while creating extra work and protracted timelines for FDA and industry.

More than Five Predicates

As noted above, AdvaMed also opposes the Working Group's proposal to prohibit more than five predicate devices. As noted by the Working Group, multiplex devices could represent more than five predicate devices' functionality. Indeed, some innovative technologies, like microarrays, could require well over the five-predicate limit. Furthermore, as devices become more complex and attempt to combine more features for both convenience and economy, the need to reference multiple predicates will increase. 510(k) sponsors should be provided the opportunity to propose and justify within the submission the use of multiple predicate devices. The effect of limiting the number of predicates could result in multiple 510(k)s where one submission would have sufficed, putting further pressure on scarce FDA resources.

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[8] *Guidance on the Center for Devices and Radiological Health's Premarket Notification Program* (*Blue Book Memo. #K86-3*) (June 30, 1986) at 13.

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Recommendation: *The 510(k) Working Group recommends that CDRH provide training for reviewers and managers on reviewing 510(k)s that use 'multiple predicates," to better assure high-quality review of these often complex devices. The training should clarify the distinction between multi-parameter or multiplex devices and bundled submissions. In addition, CDRH should more carefully assess the impact of submissions for multi-parameter or multiplex devices and bundled submission on review times, and should consider taking steps to account for the additional complexity of these submissions as it establishes future premarket performance goals.*

AdvaMed supports reviewer training on submissions with multiple predicates, and on the current bundling guidance. We further recommend that similar training be offered to the manufacturing community to ensure high-quality, consistent 510(k) submissions for CDRH to review. AdvaMed offers to partner with CDRH to conduct workshops to disseminate such training to the medical device manufacturing community.

Also, please note that, bundling is a useful and efficient submission and review method, particularly in the IVD arena. For example, if a manufacturer of diagnostic instruments makes a change to a family of instruments, CDRH can review the change only once, instead of multiple times. Likewise, a reagent for use on multiple instruments within a family could be adequately reviewed once. For IVDs, for which a Pre-IDE meeting that discusses the content of the bundled submission has been held, a well-written single 510(k) can be efficiently reviewed and cleared within the current 90-day performance goal.

Recommendation: *The 510(k) Working Group further recommends that CDRH conduct additional analyses to determine the basis for the apparent association between citing more than five predicates and a greater mean rate of adverse event reports, as shown in Section 5.1.2.3 of this report.*

AdvaMed does not support the analyses proposed by the Working Group because we believe that there is no basis to correlate adverse event data to the number of predicates in a submission, as the Working Group did in their report. FDA is implying that it has the ability, through the 510(k) process, to reduce the mean rate of adverse event reports by reviewing several step-wise 510(k)s for a product with multiple predicates, rather than one 510(k) for a product with multiple predicates. AdvaMed does not understand this reasoning, as submission and clearance of 510(k)s are based on data and evidence, which should be the same whether multiple 510(k)s or a single 510(k) is submitted.

Regarding the greater mean rate of adverse event reports for devices with multiple predicates, we recommend that a formal investigation and determination of root cause of the adverse event be undertaken before inferring that the 510(k) process is responsible.

Recommendation: *CDRH should reform its implementation of the de novo classification process to provide a practical, risk-based option that affords an appropriate level of review and regulatory control from eligible devices.*

Recommendation: *The 510(k) Working Group recommends that CDRH revise existing guidance to streamline the current implementation of the de novo classification process and clarify its evidentiary expectations for de novo requests. The Center should encourage pre-submission engagement between submitters and review staff to discuss the appropriate information to provide to CDRH for devices eligible for de novo classification, potentially in lieu of an exhaustive 510(k) review. The Center should also consider exploring the possibility of establishing a generic set of controls that could serve as baseline special controls for devices classified into class II through the de novo process, and which could be augmented with additional device-specific special controls as needed.*

AdvaMed strongly supports (1) revision of existing guidance on the *de novo* classification process; (2) pre-submission meetings to discuss data requirements for a *de novo* classification; and (3) a generic set of special controls that can be augmented with device-specific special controls as needed. Strengthening and optimizing the *de novo* process through a well-defined regulatory pathway will benefit the Agency, industry, and patients. This under-utilized process has the potential to play a key role in the regulation of medical devices lacking a predicate for which general or special controls provide a reasonable assurance of safety and effectiveness. Indeed, if CDRH were to adopt a risk-based approach, some products that are currently subject to PMA could potentially be more efficiently and effectively reviewed through the *de novo* process.

AdvaMed recommends that FDA eliminate the need to submit a 510(k) and receive an NSE determination before requesting *de novo* down-classification, so that it becomes a "one-step" process, rather than a two-step process. As part of the one-step process, FDA should implement use of a pre-review process for a *de novo* submission (i.e., a "Pre-IDE"), where FDA and the sponsor agree to use of the *de novo* process as a viable pathway as well as to the content requirements of the *de novo* submission. Early utilization of a scientific panel of experts, when needed, could benefit this pre-review. We suggest that the sponsor requesting the *de novo* classification provide completed hazard analyses in the "Pre-IDE" document and a decision-making matrix, or algorithm, using FDA-recommended templates, which could be based on current ISO 14971. The content of the *de novo* should include supportive evidence to allow the Agency to fully evaluate the risks and benefits of the device. Clinical trials or clinical data should not be an automatic requirement of a *de novo* submission; however, the hazard assessment and decision-making matrix should clearly document whether these studies are required.

AdvaMed recommends that the existing guidance for assessing the eligibility of devices for *de novo* review be revised to include the following information:

1. A determination of whether the device has a different intended use or the same intended use but has new technology as compared to the named predicate device(s) that raises different questions of safety and effectiveness.

2. A hazard analysis and Special Controls document template, including reference to ISO 14971 - *Medical devices -- Application of risk management to medical* devices *for assessing the types of risks associated with new technologies or those associated with a new intended use.*
3. A flowchart with key decision criteria (similar to the flowchart used in "Deciding When to Submit a 510(k) for a Device Undergoing a Change" guidance). We note that OIVD already employs the use of a similar flow chart.
4. We suggest that the flowcharts include the following (this list is not inclusive):
   a) Is the device a prescription device, over-the-counter (OTC), or point-of-care (POC) device?
   b) Are there existing clinical data on the use of this device (e.g., outside of the U.S.)?
   c) Identify any hazards that the device poses to individual or public health.
   d) Identify the probability of harm.
   e) Does the device directly diagnose a particular disease or condition or is the device used in conjunction with other tests to establish an overall understanding of the clinical condition of patient?
   f) What is the likelihood that the device could malfunction or the malfunction could be undetected?
   g) What is the severity of harm if the device malfunctioned or was misused? Are there general or specific controls available to reduce the likelihood or severity of the malfunction? What are they?
   h) Will a new special control guidance document reduce the likelihood or severity of harm?
   i) If, with special controls, the likelihood of the malfunction to occur is high, and the severity of harm is high (death or serious injury), then not eligible for *de novo* classification.
   j) If special controls will significantly reduce the likelihood of malfunction and greatly limit severity of injury, then review as *de novo*.

As identified in FDA's 510(k) report, a generic set of special controls for devices reviewed under the *de novo* process could be a good step to strengthening and streamlining the process and providing clear parameters at the outset. A generic set of special controls more like the essential principles of the Global Harmonization Task Force (GHTF) would provide a means to create a consistent evidentiary standard for *de novo* reviews, and would minimize movements toward the full PMA set of requirements "as is appropriate because the *de novo* process was intended to be an alternative process for FDA to classify the device into Class I or Class II. To increase consistency in the process, we recommend the creation of a template identifying these generic special controls, as well as consideration of a standard submission format similar to the Global Harmonization Task Force Standard Technical Document (GHTF STED) format. Moreover, to the extent these generic special controls replace the product-specific special controls currently required under the *de novo* process, we encourage CDRH to publish detailed decision summaries

that provide industry with sufficient detail to understand CDRH's specific thinking related to specific devices. Further, to increase the efficiency of the *de novo* process, we recommend clear guidance on how to effectively use a Pre-IDE meeting in the context of the *de novo* process. As noted previously, elimination of the current process of having to file a 510(k) and receive an NSE determination as a pre-requisite to filing a *de novo* request would streamline the process considerably.

Again as noted in FDA's report, we agree there is merit in minimizing the time spent on the 510(k) review for a product that clearly is *de novo*. The review should focus on what in addition may be needed for the next level review. The evidentiary expectations for classification should be clearly communicated to the applicant, including the use of pre-submission meetings, where appropriate. The use of a generic set of special controls more like the GHTF principles would assist in focusing and clarifying this process.

Lastly, because of the importance of developing this pillar of FDA's regulatory framework, we recommend the Agency consider holding a public meeting on this process and working with the industry and other stakeholders to optimize this process.

2. Well-Informed Decision Making

RECOMMENDATION: *CDRH should take steps through guidance and regulation to facilitate the efficient submissions of high-quality 510(k) device information, in part by better clarifying and more effectively communicating its evidentiary expectations through the creation, via guidance, of a new "class IIb" device subset.*

Unreported Device Modifications

Recommendation: *The 510(k) Working Group recommends that CDRH revise existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k), and, for those modifications that do warrant a new 510(k), what modifications are eligible for a Special 510(k).*

AdvaMed supports the recommendation to update the existing guidance (K97-1) to clarify what types of modifications do or do not warrant submission of a new 510(k). While we agree this guidance is due for a review/update, this is a good guidance that has proved useful to FDA and industry over the years. At CDRH's request, AdvaMed submitted suggestions for improvements to the guidance in May 2010. We noted that the use of flow charts to assess changes has been especially helpful and provided input on what areas needed clarification. Consideration of the risk evaluation process as a means to assess changes rising to the level of a new filing is recommended.

The 510(k) Working Group, in its description of the history of Section 510(k), describes the implementation of the New 510(k) Paradigm. In addition to the information provided in the Preliminary Report, it is important to recognize that the 510(k) Paradigm was introduced at a period in time when the CDRH review process had slowed down to such a degree that serious concerns were raised that public health was not being promoted and innovation was being stifled. In response, CDRH developed a number of means, of which the Special 510(k) was one, to obtain essential information on device modifications, while imposing the least possible burden on industry and the Agency to enable protection of the public health. It also is noteworthy that FDA received the Hammer Award for Re-invention of Government from the Clinton Administration, in recognition of the importance and value of this initiative. AdvaMed believes the current process has merit; that it adequately protects the public health while encouraging innovation.

In support of its recommendation to identify the modifications that are eligible for a Special 510(k), the FDA Working Group cites Medical Device Report (MDR) data from CDRH's databases that suggest the MDR rate for devices that were cleared through the Special 510(k) process is slightly higher than for Traditional or Abbreviated 510(k)s. As noted, CDRH believes that the total number of MDRs likely is under-reported and that MDRs frequently do not cite the 510(k) number of the device associated with the adverse event. The conclusion reached is that further analysis would need to be conducted. AdvaMed believes it is premature to reach any conclusion about the effectiveness of the Special 510(k) or limiting the devices whose modifications are eligible for Special 510(k).

AdvaMed does not agree that the MDR data accurately reflect the Special 510(k) process. FDA has recognized that the reporting system, as good as it is, is limited. Likewise, information presented by Professor Ralph Hall to the Institute of Medicine (IOM) for its review of the 510(k) process indicates that MDR data are not good tools to judge performance of the 510(k), for the following reasons: highly variable reporting rates, reporting of inaccurate information, reporting of unconnected events, lack of quality control, and lack of confirmation. Hall suggests that recall information may be a better indication.

Professor Hall, in his assessment of the 510(k) process, looked at the relationship between Class I recalls and 510(k)s. He found that only 0.22% of Class I recalls were associated with 510(k) and related to premarket issues. Professor Hall did not find a relationship between Special 510(k) and Class I recalls. Interestingly, he found a similar rate of Class I recalls for devices subject to Premarket Approval. Dr. William Maisel, formerly of the Medical Device Safety Institute at the Beth Israel Deaconess Medical Center, who also looked at recalls, found a slightly higher rate of recalls associated with devices subject to Special 510(k)s. Combined with Professor Hall's data, this would indicate that the higher rate of recalls for devices subject to a Special 510(k) were not Class I recalls, but Class II or III recalls, representing moderate or minimal risk to public health. A report commissioned by AdvaMed and conducted by the Battelle Institute (Attachment A), confirms that the risk of recall related to use of the Special 510(k) process is not significantly higher than 510(k) products cleared through relative to CDRH's other review pathways.

As noted above, there are definite benefits associated with the use of the Special 510(k), most importantly the appropriate allocation of FDA resources for review of minor modifications to manufacturers' own devices. Design control requirements ensure that companies perform and document a thorough analysis of risks and potential risks associated with a specific device and have risk management programs to mitigate all risks. Companies also have a great deal of information, including information available to FDA, regarding the prior generations of the device. This information is used as inputs into the design control process. All of the information within the Design History File is available to FDA during routine inspections of manufacturers and FDA can, if needed and it is germane to the issue of substantial equivalence, request this information as part of any premarket review process. However, either limiting the scope of the Special 510(k) process or routinely requesting this information could impose an unnecessary burden on CDRH and the industry, without any corresponding benefit.

Recommendation: *The 510(k) Working Group further recommends that CDRH explore the feasibility of requiring each manufacturer to provide regular, periodic updates to the Center listing any modifications made to its device without the submission of a new 510(k), and clearly explaining why each modification noted did not warrant a new 510(k). The Center could consider phasing in this requirement, applying it initially to the "class IIb" device subset described in Section 5.2.1.3, below, for example, and expanding it to a larger set of devices over time.*

AdvaMed does not support this recommendation for all Class II devices. This recommendation by the Working Group does not address the fundamental root causes identified in the discussion of unreported device modifications leading to the Working Group's recommendation. The examples cited, such as misuse of the Special 510(k) process, are more appropriately addressed within the Agency's current guidance, specifically the conversion of Special 510(k)s to Traditional 510(k)s, and compliance enforcement actions for extreme cases, as described in the Case Study: Unreported Modifications (pp 68-69).

The recommendation may be appropriate, provided that the definition of "any modifications" is narrowed and made relevant to changes with unclear impact on safety or effectiveness, in the context of a small, focused subset of Class II devices. It is not warranted for all Class II devices, or for the "Class IIb" subset proposed by FDA.

The periodic update is not necessary for all Class II devices, (see attached AdvaMed proposal on a small, focused subset of Class II devices, Attachment C), and would impose an unnecessary burden on FDA resources and on industry. It is the responsibility of the 510(k) holder to determine what modifications require a new 510(k) based on regulation and guidance, and FDA currently has a means to evaluate the appropriate reporting of device modifications through the facility inspection program. Changes to a device are routinely reviewed in the course of an FDA inspection of a company's design control procedure and other Quality System Regulation requirements. Revised guidance (K97-1), reflecting FDA's current thinking on device modifications that require a new 510(k), would also aide appropriate decision-making.

Quality of Submissions

Lack of Clarity

Recommendation: *The 510(k) Working Group recommends that CDRH consider adopting the use of an "assurance case" framework for 510(k) submissions. An "assurance case" is a formal method for demonstrating the validity of a claim by providing a convincing argument together with supporting evidence. It is a way to structure arguments to help ensure that top-level claims are credible and supported. If CDRH pursues this approach, the Center should develop guidance on how submitters should develop and use an assurance case to make adequate, structured, and well-supported predicate comparisons in their 510(k)s. The guidance should include the expectation that all device description and intended use information should be submitted and described in detail in a single section of a 510(k). The guidance should also clearly reiterate the long-standing expectation that 510(k)s should describe any modifications made to a device since its previous clearance. CDRH should also develop training for reviewers and managers on how to evaluate assurance cases.*

AdvaMed does not support this recommendation. Adopting the general use of assurance cases is premature and unwarranted. As the Working Group points out in its recommendations, the assurance case framework is not widely used in the medical device industry, either by industry or by FDA. This raises two immediate concerns to industry. First, given that the Working Group clearly indicates that lack of adequate reviewer and industry training is a general concern relevant to the current perceived inconsistency of 510(k) reviews, this would impose yet another new training requirement on a Center that is already struggling to ensure adequate training of existing and new staff. The second concern is that it is not clear what problem is leading FDA to make this recommendation and whether the assurance case is the only or best means of addressing the concern raised by FDA.

The example FDA cited in support of using assurance cases is one where a labeling change in an earlier generation of device was not sufficiently highlighted by the submitter and the reviewer overlooked the change in making a substantial equivalence determination. The Working Group states that all intended use information should be submitted and described in detail in a single section of the 510(k). That simple recommendation would be easy to implement and would require very little in the way of additional training for reviewers or industry. The FDA Working Group also repeats the long-standing expectation that 510(k)s should describe any modifications made to a device since its previous clearance. Even without the use of an assurance case, these two simple changes would provide that any modifications to a device would appear in two sections of any future 510(k), thus limiting the likelihood that assurance cases would be overlooked by FDA reviewers. The FDA has not made the case that they will improve 510(k) submissions for simpler devices. Nor have they made a case for why change is necessary.

Recommendation: *The 510(k) Working Group further recommends that CDRH explore the possibility of requiring each 510(k) submitter to provide as part of its 510(k) detailed photographs and schematics of the device under review, in order allow review staff to develop a better understanding of the device's key features. Currently, CDRH receives photographs or schematics as part of most 510(k)s; however, receiving both as a general matter would provide*

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review staff with more thorough information without significant additional burden to submitters. Further, CDRH could include photographs and schematics, to the extent that they do not contain proprietary information, as part of its enhanced public 510(k) database, described below, to allow prospective 510(k) submitters to develop a more accurate understanding of potential predicates. Exceptions could be made for cases in which a photograph or schematic of the device under review will not provide additional useful information, as in the case of software-only devices. CDRH should also explore the possibility of requiring each 510(k) submitter to keep at least one unit of the device under review available for CDRH to access upon request, so that review staff could, as needed, examine the device hands-on as part of the review of the device itself, or during future reviews in which the device in question is cited as a predicate.

AdvaMed does not support requiring the submission of detailed device photographs or schematics nor does it support the release of detailed photographs and other graphic depictions to the enhanced 510(k) database. It is important to acknowledge that the release of any confidential or proprietary information to the public must be done with the permission of the owner of the information, in this case, the sponsor of the 510(k) submission. Schematics generally provide engineering information (e.g., wiring diagram) that is usually considered proprietary. The same could be said of □detailed□photographs depending on the level of detail required. Any photographs or graphic depictions of a device that would provide proprietary information to competitors, both domestic and outside the United States, therefore, should not be released to a publicly available website.

AdvaMed recognizes that having a visual image of the device under review may benefit the review process and we support the submission of photographs and drawings of the device (showing the external features) that are necessary to establishing substantial equivalence. As stated in the CDRH Preliminary Internal Evaluation, many companies currently provide depictions of the device under review. However, it is important to note that at the time of 510(k) submission, the final version of the device may not be available. In addition, there are some device types, such as software, for which a schematic or photograph is not relevant. Where appropriate, CDRH may ***request*** a photograph or graphic depiction of the device under review as a means to aid the review process and serve as an educational tool, but not state it as a requirement.

AdvaMed does not support *requiring* each 510(k) submitter to keep at least one unit of the device under review available for CDRH to access upon request. Under limited circumstances AdvaMed supports *requesting* submitters to keep one unit of the device available as a sample for CDRH to see during the 510(k) review process with the understanding that the device is used for education of the reviewer, is not appropriate for testing, and that the request does not delay the review of the submission. AdvaMed recommends that the request be made only when seeing the actual device is necessary for determining substantial equivalence, with FDA developing criteria and sharing them with the industry for when such a request for a device is appropriate. When a request is made, CDRH must consider the logistics related to such a request. Delivering large pieces of equipment to FDA facilities makes little sense. Large pieces of equipment will require loading dock/receiving areas as well as secure storage within an appropriate storage

environment. At any one time, CDRH could have thousands of devices requiring storage at the White Oak facility. If CDRH expects equipment to be operational, it may require special installation and calibration activities. It is also important to be mindful that in some cases it would be necessary for the reviewer to examine the device at the manufacturing facility because of device size or installation requirements. Devices such as X-ray equipment, robotic surgical equipment, and sterilization equipment would be expensive to ship, require installation by specialized technicians, and would occupy a large amount of space at CDRH.

In addition, keeping a device available indefinitely so it can be examined when it is cited as a predicate is impractical for industry and would provide limited benefit. Providing the space necessary to ensure secure storage with appropriate environmental conditions would present a financial and logistical burden on industry, especially on small companies with limited facilities, with no commensurate benefit to public health. Indefinite retention of devices, especially IVD products, with limited shelf-lives would not provide an accurate representation of the device after the use-before date has passed. In some cases, minor changes are made to devices during their marketed life. Retaining a sample of each version of the device would add to the storage burden.

CDRH also must recognize that a device sample submitted during 510(k) review might not be a product of the standard manufacturing process, but may be a manufacturing equivalent prototype or functional model. As noted, in some cases, the device in its final form may not exist at the time of 510(k) submission. In some cases, manufacturers may not be "in production" of a device that is not cleared by CDRH. Due to the many logistical issues as well as the possibility that a device may not be in its final configuration or not available at all, AdvaMed recommends that the availability of a sample device during the review be a CDRH *request* and not a requirement.

Improper Recognition of Standards

Recommendation: *The 510(k) Working Group recommends that CDRH provide additional guidance and training for submitters and review staff regarding the appropriate use of consensus standards, including proper documentation with a 510(k). CDRH should also consider revising the requirements for "declaration of conformity" with a standard, for example by requiring submitters to provide a summary of testing to demonstrate conformity, if they choose to make use of a "declaration of conformity."*

AdvaMed strongly supports the recommendations that CDRH provide additional guidance and training for industry and review staff regarding the appropriate use of consensus standards, including proper documentation within the 510(k).

Numerous domestic and international consensus standards address aspects of safety and/or effectiveness relevant to medical devices, and many of these standards have been developed with the participation of CDRH staff. A person required to submit a 510(k) must provide information as required by the statute and regulations to allow CDRH to make an appropriate decision regarding clearance of the device. Conformance with recognized consensus standards plays an important part in satisfying some or all of these premarket review requirements.

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Current guidance[9] states "CDRH believes that conformance with recognized consensus standards can support a reasonable assurance of safety and/or effectiveness for many applicable aspects of medical devices." For 510(k)s, information on conformance with recognized consensus standards helps to establish the substantial equivalence of a new device to a legally marketed predicate device. This information may be used to show that the new device is as safe and effective as the predicate in the areas covered by the standards. Moreover, if any premarket submission includes a declaration of conformity to recognized consensus standards that contain pass/fail criteria, this declaration should, in most cases, minimize the need for CDRH to review the actual test data for those aspects of the device addressed by the standards.

Existing FDA guidance on "Recognition and Use of Consensus Standards"[10] also addresses many of the issues noted in the 510(k) Report, and additional education on these topics would be particularly helpful to industry and FDA review staff:

- Conformance to a standard may not address all safety and efficacy questions about a device
- Only certain aspects of the standard may be recognized by FDA
- What documentation is needed regarding the appropriate use of standards, and any deviations from the standard
- Appropriate use of "declarations of conformity," with inclusion of the testing results, if the standard does not include pass/fail criteria

AdvaMed does not support revising the requirements for "declaration of conformity by requiring submitters to provide a summary of testing to demonstrate conformity. The guidance clearly notes that falsifying a declaration of conformity is a prohibited act under Section 301(x) of the Act. Therefore, requiring all submitters to provide a summary of testing to demonstrate conformity, even when the standard contains pass/fail criteria, is unnecessary, and would undermine the basic tenet of the Abbreviated 510(k) process, which is another important and valuable part of the 510(k) program.[11]

With the increased move toward globalization, AdvaMed urges FDA to continue to be involved in the standards development process and to formally recognize consensus standards early and to the fullest extent possible. We also strongly support the recommendations that CDRH provide additional guidance and training for industry and review staff regarding the appropriate use of those consensus standards, including proper documentation within the 510(k). We encourage CDRH to provide more concise examples of how manufacturers may be inappropriately using the standards, and how they might use them more effectively.

Incomplete Information

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9 Guidance for Industry and FDA Staff Recognition and Use of Consensus Standards. September 17, 2007.

10 Ibid.

11 See Section 514

Recommendation: *The 510(k) Working Group recommends that CDRH should consider revising 21 CFR 807.87 to explicitly require 510(k) submitters to provide a list and brief description of all scientific information regarding the safety and/or effectiveness of a new device known to or that should be reasonably known to the submitter. The Center could then focus on the listed scientific information that would assist it in resolving particular issues relevant to the 510(k) review.*

AdvaMed does not support this recommendation for all submitters to provide this information. In its preliminary internal evaluation report, the FDA Working Group did, in fact, recognize that it *may* be necessary for a submitter to include clinical or other scientific information (emphasis added). This statement suggests that it will not always be necessary for this information to be provided. Applying this requirement automatically to all Class II devices and those Class I devices on the reserve list is excessive and suggestive of current PMA requirements (potentially eroding the distinctions between 510(k) and PMA).

AdvaMed is concerned that the Working Group proposal requests not only information that the 510(k) sponsor knows, but also all scientific information regarding the safety and/or effectiveness that should be reasonably known to the sponsor. This reflects the PMA standard for information on safety and effectiveness, not the 510(k) standard for showing substantial equivalence. This standard departs from the substantial equivalence determination established by law in Section 513(i) of the Act by implying that a full review of safety and effectiveness would be required. In addition, the language is too vague for industry to provide a consistent set of information to CDRH in any given 510(k) filing. Without a clear and reasonable definition of CDRH expectations, the 510(k) sponsor would not know whether they have met the requirement until they receive feedback under the 510(k) process from CDRH. The 510(k) sponsor also would be limited in the amount of information available for a predicate device that was not their own design.

In addition, routine submission of both a listing and a description of all scientific information for all 510(k)s would be burdensome on both industry and CDRH, with unclear benefit. As discussed elsewhere within these comments, Least Burdensome requirements do apply to 510(k) submissions and should be applied to this specific recommendation.

The example CDRH provides in its report for the need for all scientific information indicates a situation where a submitter omitted data from three clinical studies that contradicted the studies submitted in support of the 510(k). Requiring submission of all scientific information for all 510(k)s is an excessive remedy that is poorly tailored to the example proffered. In fact, this example is adequately covered by the Truthful and Accurate Statement that companies are required to sign with each 510(k) submission. Most companies understand well the implications of submitting a false statement of truthfulness and accuracy and are quite diligent at assuring that the totality of information submitted in a 510(k) accurately represents the safety and effectiveness of the new device. One must assume that, in an extreme situation like the one depicted by FDA, where a company knowingly excludes information that is relevant to substantial equivalence and directly contradictory to the data submitted in the 510(k), FDA will

take action against the company based on its failure to meet the requirements of the Truthful and Accurate Statement.

A final consideration for CDRH is whether a requirement for all scientific information could be implemented without statutory change. AdvaMed recognizes that FDA may request any information regarding safety and effectiveness about a device under review when that information is necessary to make the substantial equivalence determination (21C.F.R. 807.87(1). However, it is not clear whether, *a priori*, a list and brief description of all scientific information regarding the safety and/or effectiveness of a new device known to or that should be reasonably known to the submitter meets this test and is necessary to the substantial equivalence determination of all 510(k)s. Therefore, AdvaMed believes that implementation of this as a pre-stated requirement for all devices would require a statutory change.

Type and Level of Evidence Needed

Recommendation: *The 510(k) Working Group recommends that CDRH develop guidance defining a subset of class II devices, called "class IIb" devices, for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting, would typically be necessary to support a substantial equivalence determination.*

AdvaMed does not support the recommendation to identify a subset of Class II devices called Class IIb. While AdvaMed supports strengthening the 510(k) process by providing enhanced transparency and predictability to the CDRH reviewer expectations for a small, focused subset of Class II devices, we are concerned that the scope of the products proposed by FDA is too broad and the proposed requirements, when considered in their totality, are overly and unduly burdensome for Class II devices.[12] AdvaMed submitted its own proposal for a small focused subset of Class II devices to the docket (see Attachment C). We would like to re-emphasize that our proposal was not meant to, nor do we expect it will, create a new classification scheme for medical devices in the United States, but rather creates an informal, small, focused subset of Class II device types for which CDRH has provided advanced notice that additional information beyond that normally provided in a 510(k) may be expected to support a substantial equivalence determination. It is important to note that the AdvaMed proposal provided suggestions for a number of additional submission requirements that could be required for a device in the subset; it did not recommend that all devices in the subset be required to comply with all enhanced requirements. Nor did it suggest that all devices for which CDRH currently requires clinical information automatically become members of the subset.

Therefore, as this proposal is further developed, we urge CDRH to focus the AdvaMed's proposal for a subset of Class II and a consideration of a risk-based guidance for evidentiary standards for specific device types. This shift would make clear that this is not a new classification scheme, but simply a risk-based guidance that provides clearer direction for

[12] In its August 31, 2010 webinar the Agency conveyed that all devices for which FDA requests clinical data would be included in Class IIb.

submissions for certain device types within the current Class II program. Because these appropriately identified devices will require additional resources by both industry and FDA, it is important that they are limited to a small number of higher risk devices where public safety will benefit from the extra expenditure of resources, otherwise the extra requirements will not be practically implementable and will detract from the focus on the truly higher risk devices.

AdvaMed believes that its proposed special controls for a small subset of Class II devices provides an opportunity to consider the down-classification of certain Class III devices with a proven track record of safety and effectiveness. The special controls would allow the Agency to establish any additional pre- and postmarket requirements that may be deemed necessary for such down-classified devices.

For any subset of Class II devices, it is necessary to define clear criteria and standards that apply, through a public notice and comment period, for determining which device types fall within this higher risk subset. The types of devices that would fall into this subset would be determined based on risk management processes, and could include certain permanent implants, life-sustaining devices, and life-supporting devices where the potential for increased concern exists such that special requirements are appropriate to assure the safety and effectiveness of these devices and to clarify data expectations for manufacturers seeking clearance for devices in these classes. As more experience is gained and the use of each device becomes well-established with a historical track record of safe and effective use, the device would be removed from the subset. However, permanent implants, life-sustaining devices, and life-supporting devices with a record of safety in clinical use or with up-to-date standards, guidance and/or special controls that have proven effective would **not** warrant placement in the higher risk subset.

We disagree with OIVD's recent public comment that all Class II *in vitro* diagnostic devices for which clinical data are required should be in the higher risk subset of Class II.[13] While the regulations at 21 C.F.R. §809.10 provide for performance data, CDRH interprets this, in many cases, to mean clinical data comparing IVD performance to whatever OIVD determines to be the "gold standard." There is little evidence to suggest that the current 510(k) contents fail to provide sufficient information to enable OIVD to clear safe and effective devices. If, in fact, any IVDs are to be a part of this subgroup, the decision should be risk based, consistent with the principles of AdvaMed's *Risk-Based Approach for the Regulation of All Diagnostics*, and be supported by evidence of significant issues with an entire category of products.

Recommendation: *The 510(k) Working Group further recommends that CDRH develop and implement training for review staff and industry regarding the delineation between "class IIa" and "class IIb."*

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[13] See transcript of August 31, 2010 CDRH webinar on the CDRH 510(k) Working Group Preliminary Report and Recommendations and the Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations.

AdvaMed does not support the recommendation to create a Class IIa and a Class IIb. AdvaMed agrees that training for review staff and industry is essential in providing safe and effective products to patients, however we disagree with the name and the concept of Class IIa and Class IIb. The names imply a new classification structure that exceeds the current statutory authority of the Agency. If a guidance for a small Class II subset of devices is developed, it must be made clear to both the review staff and industry that this is not considered device reclassification or creation of a new classification scheme. Once the criteria and process for a "small subset of Class II" is developed and is subject to notice and comment, AdvaMed encourages training of review staff and industry on the application and implementation of relevant guidances.

Clinical Information

Recommendation: *The 510(k) Working Group recommends that CDRH, as part of the "class IIb" guidance described above, provide greater clarity regarding the circumstances in which it will request clinical data in support of a 510(k), and what type and level of clinical data are adequate to support clearance. CDRH should, within this guidance or through regulation, define the term "clinical data" to foster a common understanding among review staff and submitters about types of information that may constitute "clinical data." General recommendations related to the least burdensome provisions, premarket data quality, clinical study design, and CDRH's mechanisms for pre-submission interactions, including the pre-IDE and IDE processes, are discussed further in the preliminary report of the Center's Task Force on the Utilization of Science in Regulatory Decision Making (described further in Section 2, below). That report also recommends steps CDRH should take to make well-informed, consistent decisions, including steps to make better use of external experts.*

AdvaMed does not agree with FDA's premise of a Class IIb designation. AdvaMed agrees that CDRH should provide greater clarity regarding the circumstances in which it will request clinical information in support of a 510(k), and what type and level of clinical information is adequate to support clearance. Although not explicitly identified by the 510(k) Working Group as an issue, AdvaMed believes that greater clarity is needed in distinguishing clinical information intended to support 510(k) clearance from clinical information supporting PMAs.

Examples of clinical information that may be used to support substantial equivalence may consist of published and/or unpublished reports on other clinical experience of either the device in question or a justifiably comparable device, results of pre-and postmarket clinical investigation(s) or other studies reported in the scientific literature of a justifiably comparable device, or results of pre- and postmarket investigation(s) of the device.

As part of the larger regulatory picture, the 510(k) submission process assures safety and effectiveness by demonstrating substantial equivalence and documenting critical aspects of device performance and mitigating risks. If Congress intended for the 510(k) process to assure safety and effectiveness in absolute terms (rather than through a comparative lens), then both the regulatory and resource requirements under this section of the Act would need to change as would resources to accompany such expectations. CDRH should keep in mind that most devices

have a long history of safe and effective use that precludes the need for clinical data or clinical evidence.

In the context of a "subset of Class II" submission, AdvaMed supports this recommendation for those devices in the subset that require clinical information to establish substantial equivalence. However, AdvaMed does not support the concept that all IVD devices for which the Office of In Vitro Diagnostics has historically requested clinical data, should be placed in the subset of Class II devices. For many IVD devices, performance information, as specified in 21 C.F.R. §809.10, is sufficient to establish substantial equivalence. The requirement for clinical data should only apply to those IVD devices that require clinical data to establish substantial equivalence because there is no acceptable comparator or because the test or technology is new and it is not possible to tie the results to a clinical condition or diagnosis.

AdvaMed supports the recommendation that CDRH define the term "clinical data." AdvaMed recommends that CDRH review the definitions for "clinical evidence", "clinical data" and "clinical evaluation" provided in the GHTF document "Clinical Evidence-Key Definitions and Concepts" (SG5/NIR8:2007). Harmonization with these definitions would foster a common understanding among not only CDRH review staff and industry but also with international regulatory agencies

Postmarket Information

Recommendation: *The 510(k) Working Group recommends that CDRH explore greater use of its postmarket authorities, and potentially seek greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices. If CDRH were to obtain broader authority to require condition-of-clearance studies, the Center should develop guidance identifying the circumstances under which such studies might be appropriate, and should include a discussion of such studies as part of its "class IIb" guidance.*

AdvaMed does not support this recommendation to "potentially seek greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices." In light of the existing authority to require postmarket studies as part of premarket special controls and through Section 522 postmarket surveillance orders, further authority is unnecessary and may lead to a proliferation of burdensome postmarket studies that add little to enhance public health.

AdvaMed supports the recommendation with modifications to explore greater use of CDRH's existing postmarket authorities for a subset of Class II devices. Under existing authorities, FDA can issue orders for post-market data through Section 522 of the Act, and in the case of special controls, under Section 513(a)(1)(B) of the Act, can require postmarket data through performance standards, postmarket surveillance, and patient registries.

Recommendation: *The 510(k) Working Group further recommends that CDRH continue its ongoing effort to implement a unique device identification (UDI) system and consider, as part of this effort, the possibility of using "real-world" data (e.g., anonymized data on device use and*

outcomes pooled from electronic health record systems) as part of a premarket submission for future 510(k)s.

AdvaMed supports UDI for medical device labels based on the option of following GS1 or HIBCC standards implemented in a risk-based manner with an appropriate implementation timeframe. We look forward to receiving a more detailed proposal in the form of a proposed rule subject to public notice and comment. It should be noted that submitters of 510(k)s may have limited or no access to device databases and electronic health record systems. We do not support exploring how data collected or associated with UDI may be used as part of the 510(k) process, as it is premature at this time, and recommend CDRH defer evaluation of this option until such time as UDI is effective.

Manufacturing Process Information

Recommendation: *The 510(k) Working Group recommends that CDRH develop guidance to provide greater clarity regarding what situations may warrant the submission of manufacturing process information as part of a 510(k), and include a discussion of such information as part of its "class IIb" guidance.*

AdvaMed supports this recommendation for only a small number of specific device types within the subset of Class II devices for which particular circumstances or conditions would require the submission of a summary of manufacturing information (e.g., manufacturing includes a unique process that is critical to the safety or efficacy of the device). Further, rather than submitting the level of detail required for PMA submissions, CDRH should clarify via guidance that only a summary (e.g., flow chart) of the manufacturing information relevant to safety and effectiveness of a device is required.

AdvaMed does not support manufacturing information being provided for any *in vitro* diagnostic device in Class II. Although in its report, CDRH indicates this requirement is appropriate for any product with lot-to-lot variability, it typically is not the manufacturing process that introduces variability.

Recommendation: *The 510(k) Working Group further recommends that CDRH clarify when it is appropriate to use its authority to withhold clearance on the basis of a failure to comply with good manufacturing requirements in situations where there is a substantial likelihood that such failure will potentially present a serious risk to human health, and include a discussion of pre-clearance inspections as part of its "class IIb" guidance.*

AdvaMed supports the recommendation to clarify when it is appropriate for CDRH to use its current authority.

There would be no benefit to the public health from withholding substantial equivalence determinations for a subset of Class II devices, or any devices, because of alleged failures to comply with good manufacturing practice requirements (GMPs) unless there is a substantial

likelihood that the failure to comply with GMPs will potentially present a serious risk to human health. Section 513(f)(5) in FDAMA was enacted in response to FDA's extra-legal creation and use of the "reference list," to withhold 510(k) clearances until FDA verified that alleged GMP violations identified in inspections were corrected. In response to this program, Congress was "concern[ed] that FDA was inappropriately using the device premarket notification process for compliance purposes."[14] "This process was unfair and denied device manufacturers an opportunity to dispute effectively FDA's allegations that firms were not in GMP compliance. FDA set itself up as judge and jury and, in essence, administratively enjoined the classification of devices . . . ."[15]

The reference list unjustifiably delayed 510(k) clearances until alleged GMP violations were remedied and the Agency re-inspected the facility to confirm remediation. This led to significant delays in substantial equivalence determinations, resulting in physicians and patients being denied the availability of new devices.[16] More importantly, GMP corrections had nothing to do with a determination of substantial equivalence (classification of a medical device). Simply put, devices were withheld from the public, in most instances, without any actual health justification.

In eliminating the reference list, Congress maintained a link between GMPs and 510(k) by permitting the withholding of substantial equivalence determinations where a non-compliance presented "a substantial likelihood that the failure to comply with [GMPs] will potentially present a serious risk to human health."[17] In other words, Congress believed that more harm would be done to the public health by withholding the initial classifications of devices than letting them go forward, unless a significant health harm related to a GMP violation was likely.

The Agency is vested with substantial enforcement authorities to ensure compliance with its laws and can prohibit the distribution of adulterated or misbranded devices. To force enforcement considerations into the premarket context would delay the entire premarket review process without a net benefit to the public. The 510(k) process is one of classification and comparison to a legally marketed device. It is not an evaluation of whether a company is in compliance with the Act, nor should it be. Indeed, the legislative history of Section 513(f)(5) states that "[c]learly, FDA has substantial authority to enforce the Act against illegal devices and the persons who market them. It is unacceptable that the Agency misuse premarket notification to avoid enforcing the Act."[18]

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14 Senate Report No. 105-43, 105th Cong. 1st Sess., at 29.

15 *Id.*

16 *See id.* (stating, "[o]ver the past five years, the FDA has withheld device classification determinations of substantial equivalence because of its belief that firms were not in compliance with good manufacturing practices.").

17 *See* "513(f)(5).

18 *Id.*

A substantial equivalence determination does not void or otherwise limit FDA exercise of its enforcement authorities under the Act nor does it empower recipients of substantial equivalence orders to introduce into commerce misbranded or adulterated devices. Congress explained that:

> FDA can find a device substantially equivalent to a predicate device and still inform the device manufacturer that . . . it should not be marketed because of the Agency's view that the device does not comply with the law in some specified respect. Then, if a person markets the device after such notice, FDA can enforce the Act.[19]

The Act describes a complete regulatory regime that includes premarket review processes and substantial authority to remove violative devices from the market, especially including those that present potential harm to the public health. Congress was fully aware of the immense authority it vested in the FDA to maintain the Congressional balance of not over-regulating devices in the premarket context, while ensuring that only safe and effective devices can be introduced into commercial distribution.

AdvaMed recommends that if the Agency determines that a substantial equivalence determination should be withheld because a GMP non-compliance presents "a substantial likelihood that the failure to comply with [GMPs] will potentially present a serious risk to human health," the target company be afforded the due process opportunity to discuss the decision with the Agency prior to the Agency taking action.

AdvaMed does not support pre-clearance inspections for the device types in the subset of Class II devices or any Class II devices. Section 510(k) is a classification provision and not an approval authority. As such, and unlike PMA safety and effectiveness determinations, pre-clearance inspections have no relevance to the substantial equivalence question.

Recommendation: *CDRH should take steps to enhance its internal and public information systems and databases to provide easier access to more complete information about 510(k) devices and previous clearance decisions.*

Product Codes

Recommendation: *The 510(k) Working Group recommends that CDRH develop guidance and Standard Operating Procedures (SOPs) on the development and assignment of product codes, in order to standardize these processes and to better address the information management needs of the Center's staff and external constituencies.*

AdvaMed supports this recommendation. AdvaMed also recommends that CDRH include a process for alerting the public (industry) when new product codes are established.

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19 *Id.*

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Recommendation: *510(k) Working Group further recommends that CDRH enhance existing staff training on the development and assignment of product codes.*

AdvaMed supports enhanced staff training on the development and assignment of product codes.

510(k) Databases

Limited Tools for Review Staff and Outside Parties

Recommendation: *The 510(k) Working Group recommends that CDRH develop a publicly available, easily searchable database that includes, for each cleared device, a verified 510(k) summary, photographs and schematics of the device, to the extent that they do not contain proprietary information, and information showing how cleared 510(k)s relate to each other and identifying the premarket submission that provided the original data or validation for a particular product type.*

AdvaMed agrees that CDRH should develop an easily searchable database that provides appropriate information to the public. AdvaMed agrees that the database should include a verified 510(k) summary. Although it was not specifically stated in the 510(k) Working Group Recommendations, the value of a reviewer decision summary was discussed in the text of the report. AdvaMed agrees with CDRH comments that publicly providing accurate and meaningful information about previous 510(k) decisions and predicate devices is essential to increasing the transparency and predictability of CDRH s 510(k) decision making. We also agree with CDRH s position that providing information about the basis for previous decisions can provide much-needed clarity about CDRH s evidentiary expectations and decision-making rationale. The decision summaries currently posted by the OIVD for IVD clearances have proven to be a valuable tool to industry. The decision summary, in combination with consistent, verified 510(k) submission summaries, would provide interested parties, including FDA reviewers, third party reviewers, clinicians, and industry with meaningful information about the subject of the 510(k) submission and the predicate device(s). A decision summary would improve consistency in 510(k) decision-making among reviewers, and when updated guidance is lacking, enable manufacturers to understand current clearance requirements for their device.

It should be noted that AdvaMed recommends eliminating the option for submitters to provide a 510(k) Statement in lieu of a 510(k) summary. This change will assure that consistent and high quality information about any new or modified 510(k) device will be readily available to the public.

AdvaMed does not, however, support the posting of photographs, schematics, and other graphic depictions of devices on the searchable database. Schematics are proprietary information and should not be posted in a publicly-searchable database. Further, photographs and other depictions submitted with the 510(k) for the purpose of establishing substantial equivalence and educating the reviewer may be cosmetically different than the marketed device, thereby causing confusion for the public. Foreign competitors may use this information to produce counterfeit

devices or to shorten device development times and speed their time to market, resulting in competitive harm to U.S. companies. Competitive advantages afforded to foreign and domestic competitors would exist even when actual proprietary information is not disclosed.

Recommendation: *The 510(k) Working Group recommends that CDRH develop guidance and SOPs for the development of 510(k) summaries to assure they are accurate and include all required information identified in 21 CFR 807.92. The Center should consider developing a standardized electronic template for 510(k) summaries.*

AdvaMed supports CDRH's development of guidance and SOPs for 510(k) summaries. In fact, in its March 19, 2010 comments to Docket No. FDA-2010-N-0054, AdvaMed recommended that FDA establish guidance to augment its regulations regarding 510(k) Summary content and ensure compliance with the requirements. We also recommended that FDA consider providing a template, to assure that the quality of information in 510(k) Summaries is consistent and complete. This template will provide information that will help companies to determine whether a particular device can be used as a predicate, as well as assisting companies in determining the data and other information they will need to include in their own 510(k)s. AdvaMed is developing a standardized format and template for 510(k) summaries, which we will be pleased to provide to CDRH for its consideration and use.

Lack of Ready Access to Final Device Labeling

Recommendation: *The 510(k) Working Group recommends that CDRH revise existing regulations to clarify the statutory listing requirements for submission of labeling. CDRH should also explore the feasibility of requiring manufacturers to electronically submit final device labeling to FDA by the time of clearance or within a reasonable period of time after clearance, and also to provide regular, periodic updates to device labeling, potentially as part of annual registration and listing or through another structured electronic collection mechanism. If CDRH adopts this approach, updated labeling should be posted as promptly as feasible on the Center's public 510(k) database after such labeling has been screened by Center staff to check for consistency with the device clearance. In exploring this approach, CDRH should consider options to assure that labeling could be screened efficiently, without placing a significant additional burden on review staff. For example, to allow for more rapid review of labeling changes, the Center could consider the feasibility of requiring manufacturers to submit a clean copy and a redlined copy of final labeling and subsequent updates, highlighting any revisions made since the previous iteration. As a longer-term effort, the Center could explore greater use of software tools to facilitate rapid screening of labeling changes. The Center should consider phasing in this requirement, potentially starting with only a subset of devices, such as the "class IIb" device subset described above, or with a particular section of labeling. CDRH should also consider posting on its public 510(k) database the version of the labeling cleared with each submission as "preliminary labeling," in order to provide this information even before the Center has received and screened final labeling.*

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AdvaMed does not support this recommendation. AdvaMed believes that the Working Group's assumption of benefits to medical professionals and device users are overstated. Collection, organization, editorial checks of redlined copy, and posting in a database by CDRH review staff will require a significant investment of resources (both human and technological) without meaningful benefit to the public health. Labeling of some devices contains information that is intended for hospitals or practitioners. Public misuse or confusion may result, if such labeling is broadly available to the public (such as how to program some electrical devices). Public posting of preliminary labeling would provide undue benefit to competitors and would inhibit U.S. innovation. AdvaMed strongly feels that dissemination of labeling to patients (direct when appropriate or through the attending clinician) and to clinicians should remain the responsibility of the manufacturer, thereby ensuring the information reaches the appropriate audience and does not cause confusion. When it is determined appropriate by a manufacturer, labeling information is provided on a manufacturer's website and is controlled by the manufacturer to maintain accurate up-to-date labeling, and if necessary, lot-specific labeling (e.g., certain IVD products).

Limited Information on Current 510(k) Ownership

Recommendation: *The 510(k) Working Group recommends that CDRH develop guidance and regulations regarding appropriate documentation of transfers of 510(k) ownership. The Center should update its 510(k) database in a timely manner when a transfer of ownership occurs.*

AdvaMed supports this recommendation and believes that the complete history of 510(k) ownership should be maintained. We believe that it will be helpful not only for the U.S., but also for U.S.-registered foreign devices. It also would be valuable for CDRH to show the full chain of 510(k) ownership.

We urge FDA to follow through on this recommendation. We also suggest that, if possible, implementation should be handled through an existing and familiar process such as registration and listing. Implementing the recommendation in this manner would place the information in an existing database, and would simplify both FDA's entry of the information and the public's access to the information.

3. Continuous Quality Assurance

Recommendation: *CDRH should enhance training, professional development, and knowledge-sharing among reviewers and managers, in order to support consistent, high quality 510(k) reviews.*

Reviewer Expertise and Experience

Recommendation: *The 510(k) Working Group recommends that CDRH continue to take steps to enhance recruitment, retention, training, and professional development of review staff, including*

providing opportunities for staff to stay abreast of recent scientific developments and new technologies. This should include increased engagement with outside experts, as discussed further in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making (described further in Section 2, below).

AdvaMed supports this recommendation. AdvaMed agrees that CDRH should continue efforts to enhance recruitment, retention, training, and development of review staff. AdvaMed agrees with the approach noted multiple times in the recommendations that proper development and delivery of appropriate training is key to the success of any organization and to successful implementation of any change. We also agree that well-designed and effectively delivered training will lead to the greatest likelihood of program success and should be directed at both CDRH staff and industry.

In addition, AdvaMed offers the following suggestions as FDA explores opportunities to enhance its training program. We believe that the "train the trainer" approach works well for adult education and that there are several groups that FDA should consider utilizing in this way. External experts from academia and FDA alumni should be considered as potential partners to fill the training needs that will result from the changes being proposed to the 510(k) program. The use of outside experts and a "train the trainer" approach will minimize the amount of CDRH managers' time needed to perform the number of training sessions that will be required to accomplish these changes.

AdvaMed recommends that staff training require testing or proof of proficiency, similar to the requirements for training industry personnel described in Quality System Regulation. We also believe that this training should be required before staff is empowered to perform reviews or assessments under any new procedures. This training would parallel industry training requirements.

Lastly, we are in complete agreement that FDA Vendor Days and other ways to familiarize the staff with various technologies are an important addition to the program. Site visits to industry should be expanded and site visits to academia should be added to the current programs. We support fully the idea that more engagement with scientific experts from all over the world would be a benefit to FDA as well as to industry.

Recommendation: *The 510(k) Working Group further recommends that CDRH consider establishing a Center Science Council comprised of experienced reviewers and managers and under the direction of the Deputy Center Director for Science. The Science Council should serve as a cross-cutting oversight body that can facilitate knowledge-sharing across review branches, divisions, and offices, consistent with CDRH's other ongoing efforts to improve internal communication and integration. The Science Council's role in improving the consistency of Center decisions is discussed in greater detail in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making.*

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AdvaMed supports the establishment of a Center Science Council comprising experienced employees and managers under the direction of the Deputy Center Director for Science to provide oversight and help assure consistency across the Center.

The process and activity of the Council must be transparent to all stakeholders. Roles should be clearly defined for this group and made publicly available.

To enhance the value the Council can provide, the Agency should ensure that the Council provides oversight to assure consistency and integrity of the 510(k) process, rather than engaging in routine decisions that may have the unfortunate effect of undermining the process. Further, the Council should not have the authority to reverse decisions.

This process for managing new scientific information **should not be used to reach recommendations applicable to individual devices without input from the entity with legal authority to market the device**. It should not replace any legally required processes such as the current consultative and appeals routes, or otherwise render these processes superfluous to substantive outcomes. The Center Science Council should be trained to understand FDA's legal authorities and processes, in order to assure that the Council focuses appropriately on "regulatory science" rather than "pure science" in providing Center oversight.

Third Party Review

Recommendation: *The 510(k) Working Group recommends that CDRH develop a process for regularly evaluating the list of device types eligible for third-party review and adding or removing device types as appropriate based on available information. The Center should consider, for example, limiting eligibility to those device types for which device-specific guidance exists, or making ineligible selected device types with a history of design-related problems.*

AdvaMed does not support the recommendation to limit eligibility for Third Party review as stated. As noted in CDRH's 510(k) Working Group Preliminary Report and Recommendations, Third Party Reviews were established under FDAMA. Medical devices are eligible for Third Party Review except as prohibited in Section 523(a)(3) of the Act, where it states, "An Accredited person may not be used to perform a review of "(i) a Class III device; (ii) a Class II device which is intended to be permanently implantable or life sustaining or life supporting; or (iii) a Class II device which required clinical data in the report submitted under Section 510(k) for the device." The current law has no other eligibility requirements, such as device-specific guidance documents, or other imposed criteria.

The purpose of the Accredited Persons Program (AKA Third Party Review) is to implement Section 523 of the Act by accrediting third parties to conduct the initial review of 510(k)s for selected low-to-moderate risk devices. The Accredited Persons Program was intended to enable FDA to use its scientific review resources for higher-risk devices, while maintaining a high degree of confidence in the review of low-to-moderate risk devices by Accredited Persons, and

to provide manufacturers of eligible devices an alternative review process that may yield more rapid 510(k) decisions.

Recommendation: *The 510(k) Working Group further recommends CDRH enhance its third-party reviewer training program and consider options for sharing more information about previous decisions with third-party reviewers, in order to assure greater consistency between in-house and third-party reviews.*

AdvaMed supports this recommendation. AdvaMed supports CDRH enhancing its third-party reviewer training program; we also recommend periodic retraining and auditing of third party reviewers.

While the 510(k) Report referenced quality issues with the Third Party Review program, it is important to note that the report cited an analysis of third party reviews during the last 9 months of 2005, a very small and potentially outdated sample of the program as it exists today.

Seven percent of 510(k)s, or in excess of one thousand 510(k)s submitted to CDRH over the last 5 years were reviewed by Third Parties, illustrating that the program remains important to both industry and the Agency, and that it should be preserved and improved as necessary. The Accredited Persons program provides a pool of trained and qualified resources, assisting the Agency in the review of 510(k)s, and in some ways, acting in the capacity of the Ad Hoc review team as noted within the 510(k) Report.

The medical device industry values the Third Party review process as described in the law, and as currently implemented by CDRH. As requested by Dr. Shuren in the Forward of the 510(k) report, AdvaMed recommends the following potential alternatives for improving the program rather than reducing the devices eligible for Third Party Review:

- The 510(k) report states, Concerns have also been raised about the level of training and experience of accredited third parties. CDRH offers training for third-party reviewers, but it is only offered every 3-4 years. FDA assessment, accreditation, and training of Accredited Persons should occur not only upon acceptance of an Accredited Party into the program, but on an ongoing, periodic basis, thereby ensuring continued qualification of the Third Party review organizations.

- FDA should periodically audit the personnel qualifications for Accredited Persons, to ensure they are equivalent to the level within the CDRH s Office of Device Evaluation.

- FDA should periodically audit each Accredited Person to ensure performance and to inspect records, correspondence, and other materials relating to Accredited Person to ensure the quality of the reviews.

- In accordance with Section 523(b)(2) of the Act, FDA may suspend or withdraw accreditation from a Third Party, after providing notice and an opportunity for an informal hearing, when a Third Party:
  1) is not substantially in compliance with Section 523;
  2) fails to act in a manner consistent with the purposes of Section 523; or
  3) poses a threat to public health.

- FDA should educate and enforce the requirement that it is a prohibited act under Section 301(y)(1) for an Accredited Person, to:

  1) submit a report that is false or misleading;
  2) disclose confidential information or trade secrets without the submitter's consent; or
  3) receive bribes or perform a corrupt act.

- The 510(k) Working Group notes that Third Parties lack access to predicate information and to new postmarket safety information, and they find it challenging to keep up with CDRH's evolving evidentiary expectation in the absence of device specific guidance. Prior to initiating a 510(k) review, the Accredited Person should contact the appropriate CDRH Office of Device Evaluation (ODE) Branch Chief (or designee) to identify pertinent issues and review criteria, obtain non-confidential predicate information such as the reviewers' decision summary for the predicate device(s), and discuss any new postmarket safety information related to this type of device. In this way, the Accredited Person will be able to stay abreast of CDRH's evolving evidentiary expectations. Posting of 510(k) summaries on a public database also will assist in keeping Accredited Persons current on evidentiary expectations.

Recommendation: *CDRH should enhance its systems and program metrics to support continuous quality assurance.*

Recommendation: *The 510(k) Working Group recommends that CDRH develop metrics to continuously assess the quality, consistency, and effectiveness of the 510(k) program, and also to measure the effect of any actions taken to improve the program. As part of this effort, the Center should consider how to make optimal use of existing internal data sources to help evaluate 510(k) program performance.*

AdvaMed endorses the idea of developing a set of metrics to assure continuous quality assurance of the 510(k) review program. We believe that metrics carefully designed to evaluate specific aspects of the program will provide clear guidance to the Agency for maintaining and improving the effectiveness of the program.

Each metric should be focused on a specific question or aspect of the program. Collectively and individually, the metrics need to be simple and unambiguous both to FDA staff and to other

stakeholders. The metrics must be pursued diligently, and the results should be made public in a timely manner.

Finally, should FDA develop a recommendation or proposal to modify the system based on the results shown by one or more of the metrics, FDA will need to demonstrate clearly the causal relationship between the recommendation and the metric. In other words, changes that FDA proposes should be traceable to results of the metrics that they establish.

Recommendation: *The 510(k) Working Group further recommends that CDRH periodically audit 510(k) review decisions to assess adequacy, accuracy, and consistency. The ongoing implementation of iReview (described in Section 5.3.2 of this report), as part of the Center's FY 2010 Strategic Priorities, could assist with this effort by allowing CDRH to more efficiently search and analyze completed reviews. These audits should be overseen by the new Center Science Council, described above, which would also oversee the communication of lessons learned to review staff, as well as potential follow-up action.*

AdvaMed is encouraged by CDRH's intent to assess the effectiveness of the review process, and to drive greater knowledge and consistency among reviewers. These periodic audits of review decisions should not be punitive and should be for the purpose of assessing the review process and ensuring consistency across the Agency, not putting the Science Council in the position of reversing earlier decisions. For that reason, if CDRH moves forward with such audits, it will be critical for CDRH to clearly define objective audit criteria and the authority of the Council and to share those criteria with staff and industry. CDRH and industry need to have the same understanding of expectations for the 510(k) program to be effective. In addition, if CDRH conducts such audits, any major lessons learned should be communicated to the industry in a timely manner, with sufficient transition time to ensure that any changes in expectations during a pending submission do not result in significant delays.

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VOLUME II-UTILIZATION OF SCIENCE IN REGULATORY DECISION MAKING

General Comments

As a science-based agency, FDA is charged with basing its decisions on valid scientific information. However, information is not science simply because it is used in decision making. Science involves the testing of hypotheses and the repeatability of experiments, not simply the collection of unverified information. While some anecdotal or new information may be true and useful, much of it will not meet standard criteria for science and may require confirmatory studies.

Specific Comments

1. Enhancing CDRH's Scientific Knowledge Base

Recommendation: *CDRH should take steps to improve its ability to readily access high-quality information about regulated products.*

Premarket Review

Interpretation of the "Least Burdensome" Provisions

Recommendation: *The Task Force recommends that CDRH revise its 2002 "least burdensome" guidance to clarify the Center's interpretation of the "least burdensome" provisions of the Federal Food, Drug, and Cosmetic Act (21 USC § 360c(a)(3)(D)(ii) and 21 USC §360c(i)(1)(D)). CDRH should clearly and consistently communicate that, while the "least burdensome provisions" are, appropriately, meant to eliminate unjustified burdens on industry, such as limiting premarket information requests to those that are necessary to demonstrate reasonable assurance of safety and effectiveness or substantial equivalence, they are not intended to excuse industry from pertinent regulatory obligations nor to lower the Agency's expectations with respect to what is necessary to demonstrate that a device meets the relevant statutory standard.*

AdvaMed does not support the recommendation to revise the current Least Burdensome guidance document. The Report (page 17) notes that the staff at FDA are concerned about their ability to require companies to submit additional data in their 510(k)s when those data have not traditionally been required for similar products. The fact that companies raise the least burdensome requirement of the law as a defense against complying with such requests or as a basis for complaints to the Ombudsman does not mean that the section of the law or the guidance developed in 2002 by CDRH are inadequate. AdvaMed agrees with the FDA s characterization of this provision that the ..goal was to streamline the regulatory process (i.e., reduce burden) to improve patient access to breakthrough technologies not lower the statutory criteria for determination of substantial equivalence.

The provisions of the Act are clear:

Section 513(a)(3)(D)(ii)
"Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as a result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval."

Section 513(i)(1)(D)
"Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such requests, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly."

It appears that the principal issue is the need for education and training of industry and CDRH staff to improve their understanding of the meaning and intent of the least burdensome provision.

Education and training of industry and staff of the least burdensome principles are appropriate steps. As noted in the report, the background of FDA "least burdensome guidance states, "[i]n order for the least burdensome approach to be successful, it is important that industry continue to meet all of its statutory and regulatory obligations, including preparation of appropriate scientifically sound data to support applications." The report further notes, "[t]hese principles are consistent with good governance in general." Rather than begin with revision of the guidance, we recommend the Agency concentrate its efforts on education and training of industry and staff on the principles of least burdensome. The guidance document issued in October of 2002 implemented provisions of FDAMA 1997 approximately five years after its enactment. It was issued as a draft subject to notice and comment, and then re-issued as a final guidance after consideration of the comments received. Continued education and training are a necessary step to ensure adequate understanding and application of the least burdensome principles and should be implemented and evaluated prior to any revision of this guidance.

FDA should communicate clearly and consistently that the least burdensome provision is meant to eliminate unjustified burdens on industry. The Agency also should emphasize that the provisions are not intended to lower the Agency's expectations with respect to what is necessary to demonstrate that a device meets the relevant statutory standard.

"Least Burdensome" is a valuable concept for not only FDA processes, but for all government regulation. In fact, the current administration has recently issued a request to all agencies asking them to work in a least burdensome fashion. Executive Order 12866 directs agencies "to foster the development of effective, innovative, and least burdensome regulations" (Section 6(a)(2)), and to "identify and assess available alternatives to direct regulation, including . . . providing

information upon which choices can be made by the public (Section 1(b)(3)). Executive Order 12866 also directs agencies to analyze potentially effective and reasonably feasible alternatives to the planned regulation, identified by the agencies or the public (including improving the current regulation and reasonably viable nonregulatory actions) (Section 6(a)(3)(C)(iii)).

Quality of Clinical Data

Recommendation: *The Task Force recommends that CDRH continue its ongoing efforts to improve the quality of the design and performance of clinical trials used to support premarket approval applications (PMAs), in part by developing guidance on the design of clinical trials that support PMAs and establishing an internal team of clinical trial experts who can provide support and advice to other CDRH staff, as well as to prospective investigational device exemption (IDE) applicants as they design their clinical trials. The Center should work to assure that this team is comprised of individuals with optimal expertise to address the various aspects of clinical trial design, such as expertise in biostatistics or particular medical specialty areas. The team would be a subset of the Center Science Council discussed in Section 4.2.1 of this report, and, as such, it may also serve in the capacity of a review board when there are differences of opinion about appropriate clinical trial design and help assure proper application of the least burdensome principle. CDRH should also continue to engage in the development of domestic and international consensus standards, which, when recognized by FDA, could help establish basic guidelines for clinical trial design, performance, and reporting. In addition, CDRH should consider expanding its ongoing efforts related to clinical trials that support PMAs, to include clinical trials that support 510(k)s.*

AdvaMed supports the development of guidance on the design of clinical trials for support of PMAs and, when necessary, 510(k)s. This guidance should address the wide range of clinical trial designs and not be limited only to randomized controlled trials. AdvaMed strongly recommends that CDRH include industry in the guidance development process thus allowing valuable input from experienced and knowledgeable industry clinical staff.

AdvaMed supports CDRH's establishment of an internal team of clinical trial experts who can provide support and advice to FDA staff as well as prospective investigational device exemption (IDE) applicants.

AdvaMed also strongly supports CDRH's involvement with the development of domestic and international consensus standards that would be recognized by FDA and provide harmonization of requirements.

Recommendation: *The Task Force recommends that CDRH work to better characterize the root causes of existing challenges and trends in IDE decision making, including evaluating the quality of its pre-submission interactions with industry and taking steps to enhance these interactions as necessary. For example, the Center should assess whether there are particular types of IDEs that tend to be associated with specific challenges, and identify ways to mitigate those challenges. As part of this process, CDRH should consider developing guidance on pre-*

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submission interactions between industry and Center staff to supplement available guidance on pre-IDE meetings.

AdvaMed supports this recommendation. AdvaMed supports efforts to improve the IDE decision making process including the evaluation and possible enhancement of interactions with industry. AdvaMed has previously submitted to FDA (April 18, 2009) an analysis of existing pre-submission meetings and recommendations for best practices as it relates to these meetings for the life-cycle of product development and approval. AdvaMed would welcome an opportunity to work with CDRH to maximize the efficiency and quality of the IDE review and decision making process.

Review Workload

Recommendation: *The Task Force recommends that CDRH consider creating a standardized mechanism whereby review Offices could rapidly assemble an ad hoc team of experienced review staff from multiple divisions to temporarily assist with time-critical work in a particular product area, as needed, in order to accommodate unexpected surges in workload. This would need to be done in such a way that ad hoc teams would only assist with work that does not require specialized subject matter expertise beyond what the team members possess. The Task Force recognizes that such an approach is only a stop-gap solution to current workload challenges, and that additional staff will be necessary to better accommodate high workloads in the long term. The Center's staffing needs are discussed further below.*

AdvaMed is pleased that FDA is addressing its capacity to respond to surges in review workload in a standardized way. CDRH has in the past drawn on knowledge and expertise from across the Center to address time-critical work or work that required a specific expertise that resided in select individuals. The process, however, was not consistent. Having a more formal process to address such needs will make the review process more predictable across review divisions. This would be particularly useful when there are potentially competing needs from different review groups.

There are four recommendations that we would like to make as this process is developed. The first is that the Agency develops a method to assure the appropriate needs and skills are identified up front. As noted in the report, this is necessary to assure that the work being requested of an *ad hoc* team is within their skill set. It is important to ensure that members of the team are adequately trained and have sufficient knowledge of the technologies and issues related to the particular devices being reviewed. The second recommendation is that the *ad hoc* team includes at least one member from the relevant reviewing branch. The third recommendation is that there is a mechanism for oversight of the work of such teams separate from the proposed review of routine reviews. We believe this is necessary to assure the consistency of review work within branches no matter who is performing the reviews and to provide a mechanism to evaluate the impact of the broader and more formal program in this arena. Lastly, we believe it is important that the creation of an *ad hoc* team to address time-critical work does not adversely

affect routine review work, especially in the review divisions from which the members of the *ad hoc* review team were selected.

Recommendation: *The Task Force recommends that CDRH assess and better characterize the major sources of challenge for Center staff in reviewing IDEs within the mandatory 30-day timeframe, and work to develop ways to mitigate identified challenges under the Center's existing authorities.*

AdvaMed believes that expending valuable Center resources to evaluate the sources of challenge for Center staff in complying with the mandatory 30-day timeframe is unnecessary. We believe that with appropriate guidance for pre-IDE meetings and with well-managed and productive pre-IDE meetings, Center staff will accommodate the 30-day timeframe. AdvaMed would welcome an opportunity to work with the Center to mitigate the challenges and increase process efficiency and quality.

Postmarket Oversight

Recommendation: *The Task Force recommends that CDRH continue ongoing efforts to develop better data sources, methods, and tools for collecting and analyzing meaningful postmarket information, consistent with the Center's FY 2010 Strategic Priorities. In addition, the Center should conduct a data gap analysis and a survey of existing U.S. and international data sources that may address these gaps. These efforts should be in sync with and leverage larger national efforts. As CDRH continues its efforts to develop better data sources, methods, and tools, it should invite industry and other external constituencies to collaborate in their development and to voluntarily provide data about marketed devices that would supplement the Center's current knowledge.*

AdvaMed supports efforts to develop additional data sources. However, continued validation of data owners, research contractors, study methods, and data sets are necessary. Criteria for the selection of data sources should be established. Data owners, research contractors, study methodologies, and data sets should be evaluated and validated for accuracy, relevancy and quality. With respect to relevance, it will be important to validate in advance which data sets are capable of answering which types of queries to ensure that inappropriate queries are not sent to data owners which could potentially result in invalid responses. There should be a periodic auditing process to ensure the continued validity of the methodologies and data sets.

Recommendation: *The Task Force recommends that CDRH conduct an assessment of its staffing needs to accomplish its mission-critical functions. The Center should also work to determine what staff it will need to accommodate the anticipated scientific challenges of the future. CDRH should also take steps to enhance employee training and professional development to assure that current staff can perform their work at an optimal level. As part of this process, the Center should consider making greater use of professional development opportunities such as site visits or other means of engagement with outside experts in a variety of areas, including clinical care, as described below. This recommendation complements the*

AdvaMed
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Center's ongoing efforts under its FY 2010 Strategic Priorities to enhance the recruitment, retention, and development of high-quality employees.

AdvaMed supports this recommendation. AdvaMed encourages CDRH to determine essential functions that support the FDA priorities of protecting public health and access to improved medical treatment and focus resources on these functions. Recruitment and training and professional development of highly qualified and motivated employees are essential to achieve CDRH goals. AdvaMed supports CDRH making greater use of site visits, including industry site visits.

Recommendation: *The Task Force recommends that CDRH continue the integration and knowledge management efforts that are currently underway as part of the Center's FY 2010 Strategic Priorities. As part of these efforts, the Task Force recommends that CDRH develop more effective mechanisms for cataloguing the Center's internal expertise, assess the effectiveness of the inter-Office/Center consult process, and enhance the infrastructure and tools used to provide meaningful, up-to-date information about a given device or group of devices to Center staff in a readily comprehensible format, to efficiently and effectively support their day-to-day work.*

AdvaMed supports this recommendation. It is essential that CDRH have the tools and infrastructure necessary to allow reviewers to access relevant internal expertise and have meaningful, up-to-date information about devices (e.g., via a 510(k) summary database).

Recommendation: *CDRH should improve its mechanisms for leveraging external scientific expertise.*

Recommendation: *The Task Force recommends that CDRH, consistent with the Center's FY 2010 Strategic Priorities, develop a web-based network of external experts, using social media technology, in order to appropriately and efficiently leverage external expertise that can help Center staff better understand novel technologies, address scientific questions, and enhance the Center's scientific capabilities.*

AdvaMed encourages FDA to establish access to a wide range of experts, including medical and diagnostic experts who understand the medicine and technology of devices. On page 8 of the Report, the Task Force expresses a finding that, "it is difficult for Center staff to tap meaningful external scientific expertise in a timely manner." The Report then recommends that FDA establish a web-based system to enable staff to interact effectively with appropriate external experts. This recommendation partially parallels a similar recommendation that AdvaMed made during the discussions of FDA's use of science in decision making and the review of the 510(k) process. Despite our belief that both FDA and industry will be well-served if FDA staff can consult with external experts, we have several concerns that can be addressed at the beginning of the process design.

The term "social media technology" is unclear to us. Social media have become an enticing Internet venue serving a variety of purposes, some positive, others negative. Social media sites also have exhibited significant security problems. While we do not believe that FDA plans to consult scientists using current, publicly-available sites, we do believe that FDA must define the goals and the parameters, especially the limits, of the anticipated interactions.

Clearly, if external experts are to be consulted on scientific issues during a product review, the consultation is likely to include a discussion of trade secrets, proprietary information, or both. FDA should establish a defined process for choosing and qualifying external experts and for ensuring that the interactions are properly scoped, limited, and balanced. FDA should ensure that input from external experts are documented in reviewer decision summaries. FDA also should ensure confidentiality of communications related to reviews. Therefore, it is vital that the system design requirements include both a high level of cyber security, secure user access controls and other administrative, technical, and physical safeguards to protect the confidentiality of the data and to prevent unauthorized use or access. These safeguards should provide the same level and scope of security as safeguards for other federal government information systems.[20] It will be both easier and less expensive to include these controls at the beginning of development as opposed to adding them along the way.

There also is concern about potential conflicts of interest. Conflict of interest applies not only to industry ties but also to academic interests and reputation. It is important to balance the vetting process to ensure a large pool of experts while also minimizing bias. The selection process for choosing external experts for the web-based network, and the names of external experts and their qualifications should be made available on the FDA website to add transparency to the process. Additionally, developing a process to ensure transparency to the sponsor when CDRH is consulting external experts is a necessary step.

Recommendation: *CDRH should establish and adhere to as predictable an approach as practical for determining what action, if any, is warranted with respect to a particular product or group of products on the basis of new scientific information.*

Recommendation: *The Task Force recommends that CDRH assess best-practices for staff engagement with external experts and develop standard business processes for the appropriate use of external experts to assure consistency and address issues of potential bias. As part of this process, the Center should explore mechanisms, such as site visits, through which staff can meaningfully engage with and learn from experts in a variety of relevant areas, including*

[20] *See, for example*, Office of Management and Budget (OMB) Circular No. A-130, Appendix III--Security of Federal Automated Information Systems (http://www.whitehouse.gov/omb/circulars/a130/a130.html), Federal Information Processing Standard 200 "Minimum Security Requirements for Federal Information and Information Systems" (http://csrc.nist.gov/publications/fips/fips200/FIPS-200-final-march.pdf), and Special Publication 800-53 "Recommended Security Controls for Federal Information Systems" (http://csrc.nist.gov/publications/nistpubs/800-53-Rev2/sp800-53-rev2 final.pdf).

clinical care. In addition to supporting interaction at the employee level, the Center should also work to establish enduring collaborative relationships with other science-led organizations.

AdvaMed supports this recommendation. AdvaMed member companies encourage visits by FDA to healthcare facilities where they may observe the use of medical devices and *in vitro* diagnostics by actual users of the devices.

2. Applying a Predictable Approach to Determine the Appropriate Response to New Science

There is a lack of clarity within and outside of CDRH about when new scientific information warrants certain types of action by the Center, particularly a change in premarket evidentiary standards.

Recommendation: *The Task Force recommends that CDRH develop and implement a business process for responding to new scientific information in alignment with a conceptual framework comprised of four basic steps: (1) detection of new scientific information; (2) escalation of that information for broader discussion with others; (3) collaborative deliberation about how to respond; and (4) action commensurate to the circumstance — including, potentially, deciding to take no immediate action. As it puts this approach into practice, CDRH should consider adopting several key principles. First, the process should allow for a range of individuals to participate in the deliberation phase, including managers and employees, to help take into consideration potentially cross-cutting issues and assure consistency in responding to new scientific information. To support this principle, CDRH should establish a Center Science Council, comprised of experienced employees and managers and under the direction of the Deputy Center Director for Science, to provide oversight and help assure consistency across the Center. Second, the process should be streamlined to allow for new information to be raised and addressed in a timely manner. Third, the process should include a mechanism for capturing in a structured manner the rationale for taking a particular course of action, so that it can be articulated clearly to staff and external constituencies and incorporated into the Center's institutional knowledge base. Fourth, the process should be designed to allow for prioritization of issues. The Center should also develop metrics to determine whether or not the new process is effective.*

It is essential that CDRH prospectively establish a process for determining what action, if any, should be taken when new information on product performance is made available. AdvaMed supports the development of the "Predictable Approach" framework for responding to new scientific information. The four basic steps, outlined by FDA, are an appropriate means of rationally and consistently managing new information that comes to light after products have been placed on the market. However, a critical first step is to assess whether the new information is scientifically valid or simply information that may not be verified or verifiable. Such assessments will govern what, if any, actions should be taken. We also agree with a key principle articulated by FDA, that the framework should allow for "a range of individuals to

participate in the deliberation phase. It is imperative, however, that this range of individuals includes representatives from industry that are the most knowledgeable in the design, manufacture, and distribution of the product in question. Similarly, it would be appropriate for the users of the product in question to be consulted during the deliberation phase.
Finally we concur that the framework should include a mechanism for capturing in a structured manner the rationale for taking a particular course of action, so that it can be articulated clearly to FDA staff and external constituencies and incorporated into the CDRH institutional knowledge base.

Recommendation: *The Task Force recommends that CDRH enhance its data sources, methods, and capabilities to support evidence synthesis and quantitative decision making as a long-term goal.*

AdvaMed supports this recommendation. CDRH must have the tools, knowledge and resources available to support their mission and goals.

3. Promptly Communicating Current or Evolving Thinking to All Affected Parties

Recommendation: *CDRH should make use of more rapid communication tools to convey its current thinking and expectations.*

Recommendation: *The Task Force recommends that CDRH continue its ongoing efforts to streamline its processes for developing guidance documents and regulation, consistent with the Center's FY 2010 Strategic Priorities. For example, CDRH should explore greater use of the "Level 1 – Immediately in Effect" option for guidance documents intended to address a public health concern or lessen the burden on industry. CDRH should also encourage industry and other constituencies to submit proposed guidance documents, which could help Center staff develop Agency guidance more quickly.*

AdvaMed supports the development of additional product specific guidance for FDA staff and industry. The increased issuance of Level 1-Immediately in Effect guidance, however, raises concerns about implementation of new expectations without adequate notice to affected stakeholders. In the real world of product submission development, there will be products in various stages of development, including submissions pending at the Agency, applications ready for submission to the Agency, and existing device trials near completion. There is a real need for notice and comment on guidance documents, and therefore the use of Level 1 guidance is best reserved for only those matters where there is an urgent and documented public health issue that must be immediately addressed. The gains in streamlining the Agency s guidance implementation process through increased issuance of Level 1-Immediately in Effect guidance seem to be modest and deny the full and rich exchange on information resulting from stakeholder involvement.

Additionally, there should be more extensive engagement in the development of guidance, such as placing FDA staff on joint teams with stakeholders, including industry, health care providers with product knowledge, and academic experts to develop first drafts of needed guidance. Although guidance documents are not legally binding on the Agency, they do represent the Agency's current thinking, 21 C.F.R. 10.115(d)(3), and are relied upon by FDA review staff, device companies and other stakeholders. Because of the importance of these documents, the Agency would be better served if it were fully informed on the issues at hand, by receiving stakeholder and individual expert feedback, prior to publishing a draft guidance document. Obtaining this type of feedback should not be limited to public meetings or workshops; the Agency could meet with selected stakeholders and experts individually, and should do so when such meetings will advance the guidance development process. *See* 21 C.F.R. 10.115(g)(1)(i) ("FDA can seek or accept early input from individuals or groups outside the Agency").

Further, to maximize the value and efficiency of the acceptance of stakeholder guidance, we recommend the Agency more clearly indicate those guidance document topics in which receipt of early draft versions will expedite the development process versus those areas in which the Agency is well down the path in developing a draft guidance document. To increase transparency, the Agency should provide feedback on information and drafts it receives from outside sources.

Recommendation: *The Task Force recommends that CDRH establish as a standard practice sending open "Notice to Industry" letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations on the basis of new scientific information. CDRH should adopt a uniform template and terminology for such letters, including clear and consistent language to indicate that the Center has changed its regulatory expectations, the general nature of the change, and the rationale for the change. Currently, manufacturers typically learn of such changes through individual engagement with the Agency, often not until after they have prepared a premarket submission. The aim of issuing a "Notice to Industry" letter would be to provide greater clarity to manufacturers, in a timelier manner, about the Center's evolving expectations with respect to a particular group of devices. Because a change in regulatory expectations would represent a change in policy, a "Notice to Industry" letter would likely be considered guidance, although it would typically be issued relatively quickly and would generally not contain the level of detail traditionally found in other guidance documents. In the interest of rapidly communicating the Center's current regulatory expectations to industry, CDRH would generally issue "Notice to Industry" letters, if such letters constitute guidance, as "Level 1 – Immediately in Effect" guidance documents, and would open a public docket in conjunction with their issuance through a notice of availability in the Federal Register. To expedite the issuance of "Notice to Industry" letters, CDRH should develop standardized templates for these letters and, as necessary, their accompanying Federal Register notices. In addition, when appropriate, CDRH should follow "Notice to Industry" letters as soon as possible with new or modified guidance explaining the Center's new regulatory expectations in greater detail and revising the guidance where necessary in response to comments received, so that external constituencies have a fuller understanding of the Center's current thinking. CDRH should also consider creating a webpage for identifying and explaining*

new information that has altered the Center's regulatory expectations, so that, across all CDRH-regulated products, external constituencies can better understand the rationale for changes in the Center's requirements.

Although we support the Agency's recommendation to establish a standard practice for Notice to Industry (NTI) letters for use in conveying information for which the Center has changed its regulatory expectations on the basis of new information, we have several concerns and recommendations.

As part of the standard practice, we recommend the Agency clearly define the types of information and circumstances in which it would be appropriate to issue a NTI. Use of NTIs to communicate changes in thinking related to product specific issues impacting safety or effectiveness has the potential to improve the current process, where currently such issues may be communicated individually to companies with products already under review. Overuse of NTIs to communicate procedural topics, such as application format, or other topics that could be addressed via Level 2 guidance will reduce the effectiveness of the NTIs and cause unnecessary complexity to the process. Clearly defining the types of content to communicate via NTIs will maximize the utility and effectiveness of NTIs.

A critical aspect of the NTI standard practice should be recognition that whenever the Agency issues a NTI, there will be products in various stages of development, including submissions pending before the Agency, applications ready for submission to the Agency, or existing device clinical trials near completion. Because of these real world situations it is important that the NTI standard practice include a mechanism for phasing in the new expectations, accepting alternate but equivalent measures and establishing implementation dates. Under current practice, issuance of a final guidance sets forth the Agency's current thinking, but recognizes that other mechanisms may exist for addressing the particular concern. This approach should continue to apply to NTIs, thus allowing a company to address the concern in another manner.

In addition to opening a docket, along with the issuance of an NTI, as recommended by the Task Force, we recommend that the Agency consider establishing a timeframe for reviewing comments submitted to the docket. Following issuance of the NTI, the Agency should work to incorporate the new information into draft guidance for review and comment within a specified period of time.

We agree with the recommendation of providing the letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations. Importantly, the Agency should use additional tools to communicate to the industry in general, so that companies contemplating moving into the particular device market have visibility to the change in Agency thinking. Specifically, we recommend posting on the CDRH website NTIs in a readily accessible manner and tagging NTIs for inclusion in the CDRH email, "What's New at CDRH Update."

Further, a webpage dedicated to topics related to new information is certainly an important step to increasing transparency and understanding. Inclusion and consolidation of the NTIs on this page, along with the standard operating procedure that governs NTI development, is recommended.

Lastly, we believe adoption of a standard process for creating and issuing NTIs should not preclude the Agency from communicating anticipated changes in thinking at a pre-IDE meeting or other pre-submission meetings if the NTI is still under review within the Agency. One can envision a situation where a company leaves a pre-IDE with an understanding of a path forward, only to receive a NTI shortly after the meeting. Steps to avoid such situations benefit the Agency and its stakeholders.

Recommendation: *The Task Force recommends that CDRH take steps to improve medical device labeling, and to develop an online labeling repository to allow the public to easily access this information. The possibility of posting up-to-date labeling for 510(k) devices online is described in greater detail in the preliminary report of the 510(k) Working Group(described further in Section 3, below).*

AdvaMed does not support the development of an on-line labeling repository. AdvaMed has expressed concerns about the feasibility and value of this recommendation in a previous comment. Further, without an understanding of FDA□s intent regarding the improvement of device labeling, we cannot support this proposal at this time.

Recommendation: *CDRH should provide additional information to its external constituencies about its process for determining an appropriate response to new science and the bases for its actions.*

Recommendation: *The Task Force recommends that CDRH develop and make public a Standard Operating Procedure (SOP) that describes the process the Center will take to determine the appropriate response to new scientific information, based on the conceptual framework outlined above. The SOP should include the expectation that when a decision is made to take a particular course of action, including a change in evidentiary expectations, the action and its basis should be communicated clearly and promptly to all affected parties. If it is not possible to provide complete detail about the basis for an action due to confidentiality concerns, Center staff should share as full an explanation as is allowable and state why a more complete explanation is not permissible. In addition, Center leadership should take steps to make sure that all employees have an accurate understanding of what information they are permitted to discuss with manufacturers, so that information that would help clarify the basis for a particular action is not needlessly withheld.*

AdvaMed suggests that all stakeholders be involved in developing the standard operating procedure. As with any process that involves and impacts multiple groups, acceptance of and conformance to the process improves when all stakeholders are involved. Importantly, the

principles we outlined in our response to the conceptual framework proposal, should also be applied to any SOPs.

Recommendation: *The Task Force recommends that CDRH continue its ongoing efforts to make more meaningful and up-to-date information about its regulated products available and accessible to the public through the CDRH Transparency Website, consistent with the Center's FY 2010 Strategic Priorities and the work of the FDA Transparency Task Force. In addition to the pre- and postmarket information that is already available on CDRH Transparency Website, the Center should move to release summaries of premarket review decisions it does not currently make public (e.g., ODE 510(k) review summaries) and make public the results of post-approval and Section 522 studies that the Center may legally disclose. Making such information readily available to the public will provide CDRH's external constituencies with greater insight into the data that guide the Center's decisions and evolving thinking.*

As stated in our previous comments, AdvaMed supports the posting of reviewer summaries on a CDRH website, however, only those summaries for cleared devices should be released. Review summaries for devices that are not cleared would reveal company confidential information that would negatively impact marketing competitiveness and at the same time, serve no public health benefit because the product has not yet been made available to the public. An NSE determination is not the end of a company's product development. A company may resubmit the 510(k), pursue the *de novo* pathway, or submit a PMA. AdvaMed has submitted detailed comments on FDA's transparency initiative (see AdvaMed comments at Docket No. FDA-20098-N-0247) that articulate our strong concerns about FDA's proposed disclosure of confidential and proprietary information. For these reasons, AdvaMed supports making public only summaries of the results of post-approval and Section 522 studies that the Center may *legally* disclose.

ATTACHMENT A

Battelle
The Business of Innovation

510(k) Premarket Notification Evaluation

Prepared By:
Battelle Memorial Institute

For:
AdvaMed

September 2010

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510(k) Premarket Notification Evaluation

1. Introduction

This report analyzes Class I recalls of medical devices which were previously cleared through the United States Food and Drug Administration's (FDA's) 510(k) Premarket Notification Process. These recalls are compared to recalls of exempted devices as well as devices approved through the Premarket Approval (PMA) process. Data were gathered from publically available information from the FDA, as well as information made available by companies with affected products.

2. Executive Summary

FDA product recalls are actions taken when FDA-regulated products are defective or potentially harmful; Class I recalls are the most serious of these recalls, and represent products that may cause serious health problems or death. Data for Class I recalls of 510(k)-cleared devices in the United States were reviewed over a 64-month period, beginning January 1, 2005 and ending May 1, 2010 (hereafter referred to as the "review period"). There were, on average, 15 unique 510(k)-cleared device recalls per year between calendar years 2005 and 2009.

There have been 46,690 devices cleared through the 510(k) process since 1998—the year certain low-risk medical devices began to be exempted from premarket notification requirements (as part of The Food and Drug Administration Modernization Act (FDAMA)). This time period was selected because gathering data back to 1976 (the enactment of the 510(k) process) would include a large number of Class I devices which were later exempted from the 510(k) process by the FDAMA. This would inflate the total number of devices cleared, reducing the percentage of significant recalls for devices. The number of clearances/approvals from 1998 through May, 2010 was used to calculate recall percentages because it was assumed to be more representative of the number of products on the market potentially subject to recall rather than only using products cleared during the 64-month review period.

In this same time period since 1998, 2,825 devices have been approved through the Premarket Approval (PMA) process. This total includes PMA supplements representing significant changes: 180-day supplements and panel track supplements. 180-day supplements which are categorized as "no user fee" are excluded, as these filings are generally for minor changes such as manufacturing location or labeling which improves or clarifies warnings or precautions.

The table below details the number of devices with recalls over the review period of January 1, 2005, to May 1, 2010. Because the enactment date of FDAMA was used to calculate the total number of devices cleared or approved, recalled devices that were cleared or approved prior to the enactment of FDAMA were excluded from the total recall count and percentage calculations. Recalls of both 510(k)-cleared and PMA-approved devices represent a fraction of a percent of all total clearances or approvals, and a smaller percentage of recalls have been associated with 510(k) clearances than with PMAs (0.16% vs. 0.85%).

Number of Cleared or Approved Devices Recalled, Compared to all Clearances and Approvals Since 1998

Clearance or Approval Type	Total Number of Devices Cleared or Approved Since 1998	Class I Recalls: Jan. 2005 – May 2010	Percentage of Total
Devices - PMA	2,825[1]	24	**0.85%**
Devices - 510(k)	46,690	77	**0.16%**

Probable causes of device recalls were assessed based on available data from manufacturers and the FDA. Several assumptions were made in this assessment, and are detailed in Sections 3 and 5. According to this analysis, approximately 50% of the recall causes of 510(k)-cleared devices in the review period were attributed to design deficiencies (representing less than 0.1% of all 510(k) clearances since 1998), 29% to manufacturing deficiencies, and 6% to labeling deficiencies. The remaining 15% of 510(k)-cleared device recall causes were classified as "design or manufacturing," as data were not available to make a determination with a reasonable degree of confidence.

In the United States, medical devices are classified into three classes, Class I, II, and III, based on the level of control necessary to assure the safety and effectiveness of the device. Recalls of Class II devices represent 61% of all device recalls over the review period, followed by Class III devices at 28%. Class III devices, which primarily follow a PMA approval pathway, have recently (CY 2004-2008) represented approximately 15% of device approval and clearance totals at the FDA. This percentage includes both original PMA applications (1%) and supplements to PMA approvals (14%), with 510(k)s for Class I, II, and III devices constituting the remaining 85%.

In summary, devices cleared through the 510(k) Premarket Notification Process result in a smaller percentage of recalls (0.16%) than PMA approved devices (0.85%), and these recalls represent a fraction of a percent of all devices cleared or approved since enactment of the FDAMA.

More detailed results of the analysis, including charts and tables, are contained in Section 3. Assumptions made in the data analysis and data collection methods are detailed in Section 5.

[1] Includes 180-day supplements (excluding "no user fee" supplements) and panel track supplements.

3. Recalls of Devices Cleared through the 510(k) Premarket Notification Evaluation

Recalls are actions by a device manufacturer to correct a problem or remove a product from the market. Class I recalls are the most serious recalls, and involve a *"situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death*[2]*".* Recalls may be conducted on a manufacturer's own initiative, by FDA request, or by FDA order under statutory authority. Class I recalls can be issued for medical devices, drugs, biologics, and food. Only a portion of medical device recalls are for devices that have been cleared through the 510(k) Premarket Notification Process.

Recall data for 510(k)-cleared devices were evaluated over an approximate five year review period, from January 1, 2005 to May 1, 2010. Recalls of PMA-approved devices are referenced for comparative purposes.

3.1. Number of Unique Recalls

United States Class I medical device recalls were gathered from the FDA's "Medical Device Recalls" database[3] on May 6, 2010, resulting in several hundred line-item recalls. Some line item recalls were then grouped with similar entries. This grouping methodology is outlined below:

- Recalls were grouped when different model numbers of the same product were recalled, provided the products were likely marketed under the same 510(k) or PMA and involved the same root cause.
- Recalls were grouped when products were re-branded for sale under different trade names, provided the products were likely marketed under the same 510(k) or PMA and involved the same root cause.
- Recalls were grouped when a recall was expanded to additional manufacturing lots of the same product for the same root cause.
- Recalls were grouped when a recall involved a single manufacturer for systemic production or quality issues over a limited time period. For example, a failure to follow Good Manufacturing Practices[4] (GMP) across several product lines.

The FDA's weekly "Enforcement Reports"[5] and the FDA's "List of Device Recalls"[6] were used to aid in this grouping process.

Device recalls were then categorized based on the devices' likely clearance or approval histories, using data available in the FDA's PMA and 510(k) databases.

Figure 1 compares the total number of Class I recalls for 510(k)-cleared devices with other device recalls over the review period of January 1, 2005, to May 1, 2010. "Other Devices" includes devices exempt from Premarket Notification or Approval, or devices marketed without receiving an appropriate clearance, approval, or exemption.

[2] United States Code of Federal Regulations, 21 CFR 7.41.
[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm
[4] United States Code of Federal Regulations, 21 CFR 110.
[5] http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm
[6] http://www.fda.gov/medicaldevices/safety/recallscorrectionsremovals/listofrecalls/default.htm

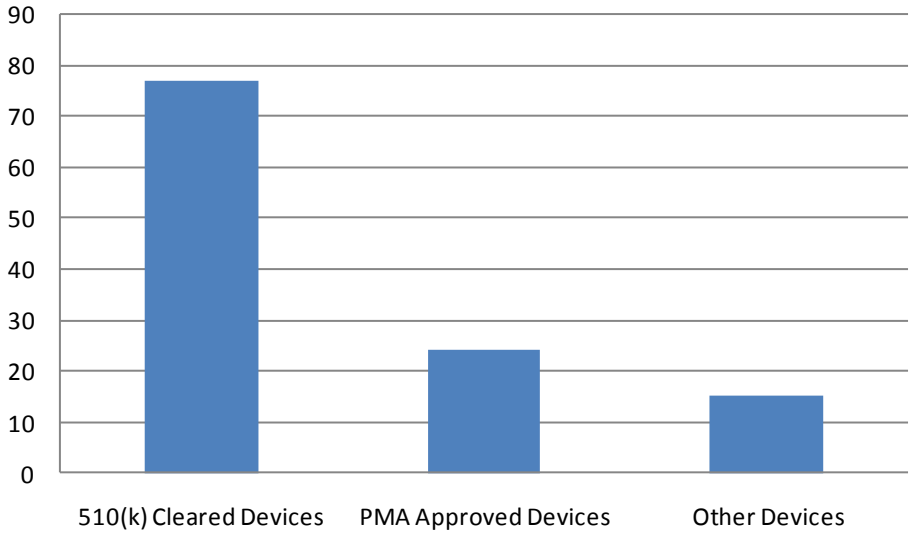

Figure 1: Number of Device Recalls.

3.2. Number of Class I Recalls Compared to the Total Number of Products Cleared or Approved

The total numbers of device clearances and approvals since 1998 were used as relative indications of the respective number of devices on the market. In 1997, the U.S. enacted the Food and Drug Administration Modernization Act (FDAMA), which represents the last major change to the FDA's clearance and approval regulations, and included a 510(k) filing exemption for certain low risk medical devices (e.g. tongue depressors). This premarket notification exemption was implemented in early 1998[7]. Table 1 below displays the percentage of devices recalled during the review period as compared to the total number cleared or approved since 1998. Devices with 510(k) clearances represent the smallest percentage of Class I recalls when compared to the total number of clearances or approvals. The PMA totals include both PMAs and PMA supplements representing significant changes: 180-day PMA supplements (excluding "no user fee" supplements) and panel track supplements.

Table 1: Number of Cleared or Approved Devices Recalled, Compared to all Clearances and Approvals Since 1998.

Clearance or Approval Type	Total Number of Devices Cleared or Approved Since 1998	Class I Recalls: Jan. 2005 – May 2010	Percentage of Total
Devices – PMA	2,825[8]	24	**0.85%**
Devices - 510(k)	46,690	77	**0.16%**

[7] On February 2, 1998, the FDA published a notice in the Federal Register announcing a list of Class I devices that it considered to be exempt from premarket notification effective February 19, 1998.
[8] Includes 180-day supplements (excluding "no user fee" supplements) and panel track supplements.

3.3. Device Recall Causes

This section presents the most likely causes of Class I recalls for 510(k)-cleared and PMA-approved devices, based on available data.

The determination of cause for some recalls was straightforward, such as a "manufacturing" cause for a device manufactured without following Good Manufacturing Practices (GMP). Other cause determinations had to be inferred through often limited information available in the recall text, press releases, and the manufacturers' published data. The "Assumptions" section, Section 5.1, details these uncertainties in greater detail.

The cause categories used for the device analysis are detailed below:

Manufacturing
These recalls include causes that were most likely related to manufacturing deficiencies. These causes may include failure to maintain sterility, failure to follow GMP, or manufacturing QC deficiencies.

Design
These recalls include causes that are likely due to flaws inherent in the design of the device, either created initially or through approved design changes (e.g., part obsolescence).

Manufacturing or Design
Recalls in this category could either be due to manufacturing or design causes. The information available for these recalls does not indicate the cause of the recall, other than the root cause was likely either in design or manufacturing. This category was employed due to frequent lack of comprehensive information provided by the FDA's recall notice and the device manufacturers. An example may include a failed electronic component, where no data are given as to why it failed; the component failure may be tied to the initial design not accounting for tolerances, or a supplier quality issue delivering out-of-specification components.

Labeling
These recalls result from a labeling deficiency (though these issues may ultimately result from a manufacturing or a design root cause).

Table 2 presents the likely cause of Class I recalls for 510(k)-cleared and PMA-approved devices, using the categories mentioned above. These causes are presented as a percentage of total devices marketed since 1998. As previously mentioned, total PMA devices include panel track supplements and 180-day supplements, excluding "no user fee" supplements. The analyses include recalls issued between January 1, 2005, and May 1, 2010.

Table 2: Percentage of Device Recall Causes, Compared to Total Number of Devices Cleared or Approved Since 1998.

Clearance or Approval Type	Recalls as a Percentage of Total Devices Since 1998	Recalls due to Design Causes	Recalls due to Manufacturing Causes	Recalls due to Labeling Causes	Recalls due to Manufacturing or Design Causes
Devices - PMA	**0.85%**	**0.46%**	**0.18%**	**0.11%**	**0.11%**
Devices - 510(k)	**0.16%**	**0.08%**	**0.05%**	**0.01%**	**0.03%**

3.4. Device Recall Requirements

A variety of impacts to devices currently on the market can occur when a Class I recall is initiated. Four categories were used in this research:

Removal from Inventory:
The device under recall was required to be removed from operation. The methods included destroying devices, returning devices to the manufacturer, or on-site removal by the manufacturer. Often, refurbished or replacement devices were provided to the customers.

Field Fix:
The device under recall could be repaired in the field, either by the manufacturer or the user. These fixes often included software upgrades or replacement components.

Labeling:
These recalls addressed a product deficiency which could be mitigated with a labeling change. Recalls initiating a labeling change may provide labeling updates electronically, through mail, or through an on-site call by the manufacturer.

Monitor for Conditions:
The requirements for these recalls included the monitoring of patients or equipment for adverse events. This included monitoring patients with potentially defective implantable devices.

Figure 2 outlines the field requirements of Class I 510(k) device recalls and Figure 3 outlines the field requirements of Class I PMA device recalls, using the categories outlined above. The review period was January 1, 2005, to May 1, 2010.

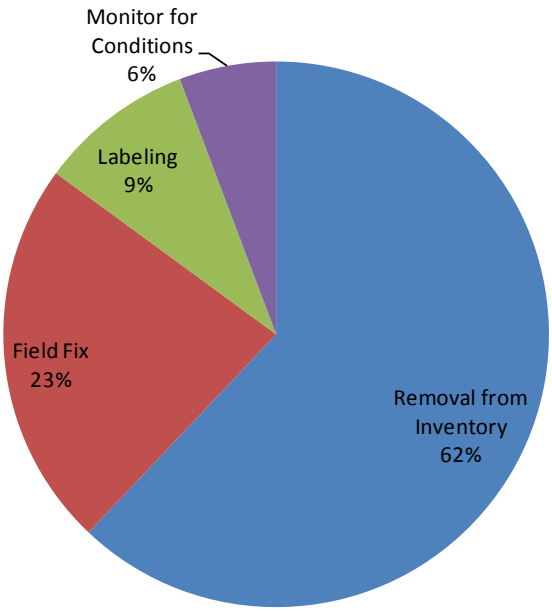

Figure 2: Field Requirements for Class I 510(k) Device Recalls.

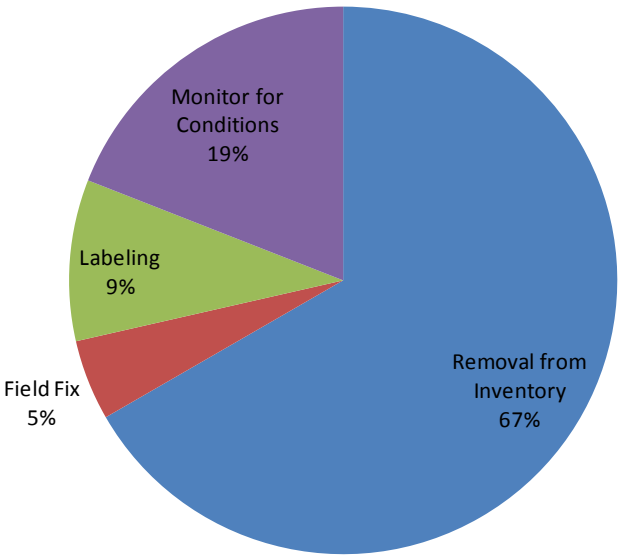

Figure 3: Field Requirements for Class I PMA Device Recalls.

3.5. Clearance and Approval History of Recalled Devices

Clearance or Approval Type

Devices that have undergone a Class I recall meet one of the following four conditions:

- The device has been cleared through the 510(k) process (Special, Traditional, or Abbreviated 510(k)).
- The device has been approved through a Premarket Approval Application (PMA).
- The device has been exempted from clearance or approval because the device is one that was in commercial distribution before May 28, 1976, the enactment date of the Medical Device Amendments.
- The device was not cleared, approved, or exempted through any of the three pathways above.

The 510(k) or PMAs associated with the recall could not always be identified with a high degree of confidence, as manufacturers and model numbers may change without notification to the FDA. In addition, manufacturers may have renamed the product or produced derivative products that did not require a separate filing. The "Assumptions" section, Section 5.1, details the methodology and assumptions used to determine the most likely 510(k) or PMA associated with the recall. Figure 4 indicates the clearance / approval history of the Class I recalled devices over the review period.

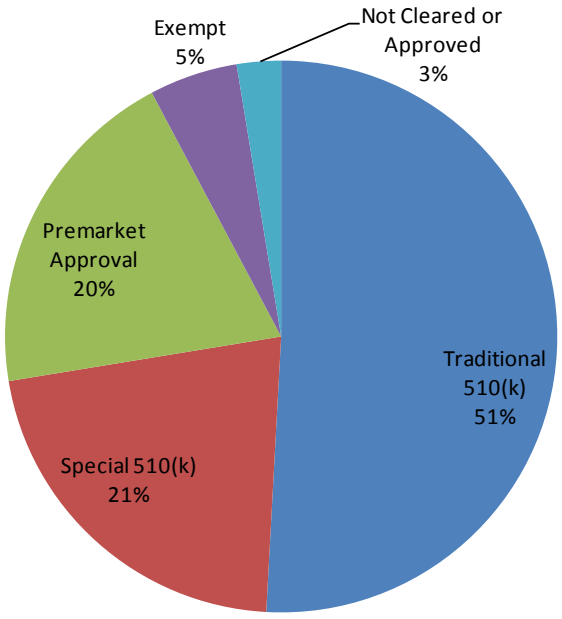

Figure 4: Clearance/Approval Routes of Class I Device Recalls.

3.6. Device Class and Type Recalled

This section documents Class I recalls by device classification, according to the FDA's classification system. The FDA has established classifications for roughly 1,700 medical devices and grouped them into 16 device panels. Each of these generic types of devices is assigned to one of three regulatory classes (I, II, or III), based on the level of control necessary to assure the safety and effectiveness of the device. Data are based off the 510(k) or PMA associated with the recalls.

Device Classification

The three U.S. medical device classes and the requirements which apply to them are:

- Class I: (General Controls)
  - With Exemptions
  - Without Exemptions
- Class II: (General Controls and Special Controls)
  - With Exemptions
  - Without Exemptions
- Class III: (General Controls and Premarket Approval)

The class to which a device is assigned determines, among other things, the type of premarketing submission/application required for FDA clearance to market. If the device is classified as Class I or II, and if it is not exempt, a 510(k) is required for marketing. All devices classified as exempt are subject to the limitations on exemptions[9]. For Class III devices, a premarket approval application (PMA) is required unless the device is on the market prior to the passage of the medical device amendments in 1976, or substantially equivalent to such a device (and PMA's have not been called for).

Figure 5 displays the device classification of Class I recalled devices over the review period. Figure 6 shows the percentage of devices cleared or approved over a 5 year period from 2004 through 2008[10] for comparative purposes; however, no data are available to indicate the number of preamendment or 510(k) exempt products placed on the market in this timeframe.

[9] Limitations of device exemptions are covered under 21 CFR xxx.9, where xxx refers to Parts 862-892.
[10] FDA ODE, Annual Performance Report, FY 2008.

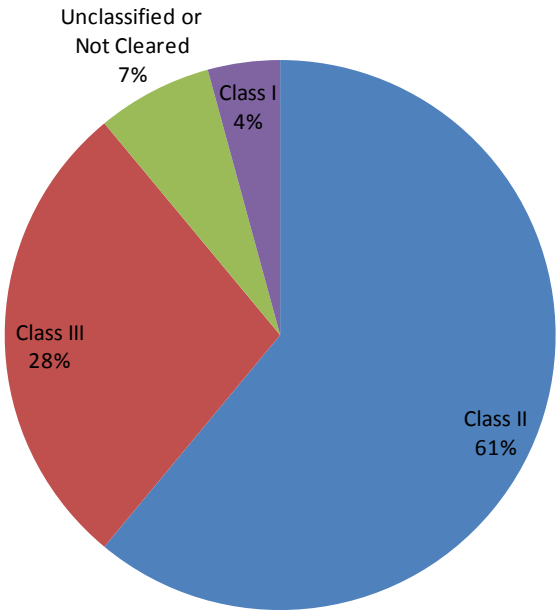

Figure 5: Device Classification of Class I Recalls.

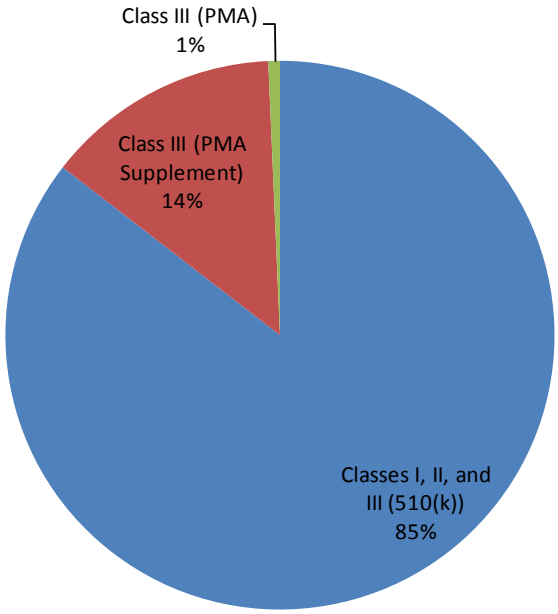

Figure 6: Device Classification of All Clearances and Approvals, FY 2004-2008 (FDA).

4. Conclusion

The number of devices with post-FDAMA 510(k) clearances that have undergone a Class I recall between January 1, 2005 and May 1, 2010—approximately 77—represents less than 0.16% of the 46,690 devices that have been cleared through the 510(k) Premarket Notification Process since 1998. This represents a significantly smaller percentage than Class I recalls of PMA approved devices at 0.85%.

5. Appendices

5.1. Assumptions

The following list outlines key assumptions made while collecting and analyzing the data presented in this report.

1. Data were based on publicly available information on the FDA's website, www.fda.gov, and a limited number of press releases and news external to the FDA's website. Data were collected from May 6, 2010 to May 26, 2010. Data from these sources were assumed to be accurate and complete.

2. Recall data—including letters to medical professionals, press releases, enforcement reports, and supplementary information—did not include data on the devices' clearance or approval histories. Therefore, the authors had to surmise the most likely 510(k) or PMA associated with each recall. In many cases, trade names and manufacturers listed in the device recalls are not the same as those listed in the devices' 510(k)s and PMAs, due in part to mergers, acquisitions, or re-branding.

3. In a majority of cases, recall data—including letters to medical professionals, press releases, enforcement reports, and supplementary information—did not provide adequate data to determine with certainty the root cause of the device recalls. In particular, determining cause between "design" and "manufacturing" was particularly uncertain; in many cases the authors had to surmise the most likely cause of the recall, or bin the data into a combined group—"Design or Manufacturing". Certain rules were used to assign recalls to particular categories. These include:

    - Failure to maintain or assure sterility: manufacturing.
    - Failure to follow GMP: manufacturing.
    - All labeling issues: labeling (whether root cause was design or manufacturing).
    - Software "bug" (except where due to failure in software manufacturing processes): design.
    - Recall of specific lots of an established product: manufacturing.

4. Similar line item recalls across a limited date range were considered to be a single recall. For example, cases where a recall was expanded to additional lots or product lines were considered to be a single recall.

5. Approximately 5% of device recalls which were not associated with preamendment or exempt devices could not be associated with a 510(k) or PMA with a reasonable degree of certainty. These recalls were not included in the tally of device class, but were included in the count of number of medical device recalls per year.

6. Because the enactment date of FDAMA was used to calculate the total number of devices cleared or approved, recalled devices that were cleared or approved prior to the enactment of FDAMA were excluded from the total recall count and percentage calculations.

5.2. Data Sources and Collection Methods

On May 6, 2010, an initial list of Class I device recalls was queried from the database located at:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm

The following search parameters were selected:

- Product name: blank
- Recall class: 1
- Recall number: blank
- Reason for recall: blank
- Recalling firm: blank
- Sort by: Date Record Posted (Descending).

From this list, recalls were combined into logical groupings, based on recall text and other available data, including the "Recall Summary" page, located at:

http://www.fda.gov/medicaldevices/safety/recallscorrectionsremovals/listofrecalls/default.htm

Once recalls were recorded and grouped, 510(k)s and PMAs associated with the recalls were researched.

For 510(k)s, the primary method of research included searching the FDA website for 510(k) summary information through an external search engine (Google). The following example search demonstrates the format that was used:

```
site:fda.gov filetype:pdf 510(k) Guidant pacemaker
```

For PMAs, the FDA's PMA database was used for research, as well as search engine queries:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

After an initial list of potential 510(k)s and PMAs were determined, the search was narrowed and modified to key-in on specific model names or features that were present in the recalled

devices. Company websites, literature, and published information were used to gain confidence that the appropriate 510(k) or PMA was selected.

Once the 510(k) or PMA had been selected, information was recorded from the submission and clearance/approval, including device classification and panel, clearance/approval date, and clearance/approval route.

ATTACHMENT B

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AdvaMed Legal Analysis of Rescission Authority

In its proposal, the 510(k) Working Group recommends:

> that CDRH consider issuing a regulation to define the scope, grounds, and appropriate procedures, including notice and an opportunity for a hearing, for the exercise of its authority to fully or partially rescind a 510(k) clearance. As part of this process, the Center should also consider whether additional authority is needed.

510(k) Working Group Preliminary Report and Recommendations at 58. Under current law, FDA does not have statutory authority to rescind a 510(k) substantial equivalence determination, and this authority cannot be implied from policy or other non-statutory grounds. Consequently, without a basis in the Federal Food, Drug, and Cosmetic Act (FD□C Act), the agency cannot promulgate regulations defining rescission authority. FDA can only nullify a finding of substantial equivalence if the 510(k) applicant committed fraud in seeking that determination or, in very limited circumstances, based on inadvertent administrative mistakes or errors by the agency.

Rescinding a 510(k) would not only reclassify a device, but would reclassify all devices that relied upon the device subject to rescission, and would do so without adhering to the reclassification requirements in the FD□C Act for new devices, *see* □513(e). Effectively, the Working Group and the Center for Devices and Radiological Health (CDRH) are using so-called rescission as an enforcement tool for removing undesirable devices from the market, instead of removing such devices through the exercise of the agency□s substantial and broad enforcement authority. If the agency believes it is important to remove a device from use and eliminate it as a predicate, under the law what FDA must do is obtain a judicial order finding a device is misbranded or adulterated, thus, eliminating the device as a predicate in the premarket notification process, *see* □ 513(i)(2). Alternatively, FDA could reclassify the device into class III, assuming the administrative record would support reclassification. Rescission is unnecessary to protect the public health, and as we discuss below, neither the agency□s bases for rescission proposed in 2001, nor its current statements support or create rescission authority.

I. FDA DOES NOT HAVE STATUTORY AUTHORITY TO RESCIND 510(K)s BASED ON SUBSTANTIVE OR POLICY GROUNDS AND CANNOT PROMULGATE REGULATIONS DEFINING THAT AUTHORITY.

A. FDA does not have authority under the FD□C Act to rescind 510(k)s.

The FD□C Act does not directly or indirectly authorize FDA to rescind substantial equivalence orders. Under that Act, Congress explicitly gave FDA the authority to

withdraw premarket approvals (PMAs) (□515(e)(1)), investigational device exemptions (IDEs) (□520(g)(5)), and product development protocols (PDPs) (□515(f)(7)). The authority to classify devices under sections 510(k) and 513(f)(1) (and later 513(i)) did not include the authority to rescind classifications. Consistent with the rule of statutory construction, if the legislature did not include withdrawal or rescission authority, it was not intended. The FD□C Act□s remedy for an incorrect classification was and is reclassification. Indeed, Congress identified separate reclassification provisions for each group of devices that were subject to classification under the Act: preamendment devices and those substantially equivalent to them (□513(e)); postamendment class III devices (□513(f)(3)); and transitional devices (□520(l)(2)). No analog to withdrawal authority exists for premarket notification orders because these orders are not approvals, *see* 21 CFR □807.97 (deeming 510(k) devices misbranded when represented as receiving FDA approval), like the administrative orders that are subject to withdrawal.

Even the fact of an approval did not by itself imply the authority to withdraw an approval. In the drug context, Congress recognized that the power to approve does not imply the power to withdraw. Specifically, in 1938, it gave FDA the power to approve new drug applications (NDAs); in 1962, it gave FDA the power to withdraw such applications. The 1962 provision would have been unnecessary if the power to approve NDAs had included or implied the power to withdraw them. If an approval did not entail the power to withdraw the approval, certainly FDA cannot through a miracle of words create withdrawal or rescission authority for a classification, particularly when the statute explicitly provides for reclassification authority.

Because premarket notification under the FD□C Act is a means of classifying devices, rescinding a 510(k) clearance would reclassify that device. Reclassification of preamendment devices, including substantially equivalent devices, is governed by section 513(e) of the FD□C Act. That provision permits reclassification through rulemaking if FDA has □new information□to justify the result. Under section 513(e), FDA may reclassify a type of class III device into class II or class I, or may reclassify a type of class II device into class I. *See* 21 C.F.R. □860.130(c). Rescinding a 510(k) would reclassify substantially equivalent class I and II devices into class III. Consequently, if FDA asserts the authority to rescind a device□s marketing clearance for any reason, at any time, the agency would be substituting its judgment for that of Congress, and would change a device□s classification in a way not anticipated or permitted under the FD□C Act. Rescission of a 510(k) device classification would be an agency-created reclassification remedy without basis in the FD□C Act.

FDA cannot promulgate regulations that exceed the authority granted to it under the FD□C Act. Section 701(a) of that Act grants FDA □the authority to promulgate regulations for the efficient enforcement of [the FD□C Act].□ However, section 701(a) does not give FDA unlimited regulatory powers; □regulations issued under that section must effectuate a Congressional objective expressed elsewhere in the Act.□ *Pharm. Mfrs. Ass'n v. FDA*, 484 F.Supp. 1179, 1183 (D.Del. 1980), *aff'd* 634 F.2d 106 (3d Cir. 1980).

In *U.S. v. Nova Scotia Food Products*, 568 F.2d 240 (2d Cir. 1977), the U.S. Court of Appeals for the Second Circuit stated that section 701(a) of the FD□C Act is □analogous to the provision □make . . . such rules and regulations as may be necessary to carry out the provisions of this Act,□ in which case the □validity of a regulation promulgated thereunder will be sustained so long as it is □reasonably related to the purposes of the enabling legislation.□□ *Nova Scotia Food Prods.*, 568 F.2d at 246 (citations omitted). The U.S. District Court for the District of Columbia pointed out that section 701 of the FD□C Act □does not constitute an independent grant of authority that permits FDA to issue any regulation the agency determines would advance the public health. Rather, □[701] permits the FDA to use rules as a means of administering authorities otherwise delegated to it by the Congress.□ *Ass'n of Am. Physicians and Surgeons v. FDA*, 226 F.Supp.2d 204, 213 (D.D.C. 2002). Because the FD□C Act does not grant FDA the authority to rescind 510(k)s, none of the agency□s regulations can express or imply such authority.

In 2001, FDA asserted in a proposed rule that its administrative procedure regulations (specifically, 21 C.F.R. □□10.33(a), (h), and 10.75) provide the authority to rescind 510(k)s. *See* 66 Fed. Reg. 3523, 3524 (Jan. 16, 2001). It is improper for the agency to rely on a regulation as authority to issue another regulation. Indeed, FDA□s regulations cannot provide it with authority that was not conferred by Congress in the first place. Without authority from the FD□C Act, FDA cannot issue additional regulations to rescind 510(k) device classifications.

B. FDA does not have implied power to rescind 510(k)s.

Understanding there was no statutory basis for rescission, FDA in the past asserted its recession authority derived from federal case law that recognizes an implied authority for agencies to reconsider administrative actions, even if the applicable statutes and regulations do not provide for reconsideration. *See* 66 Fed. Reg. at 3524. However, that case law provides a narrow implied authority for tribunals to reconsider actions before the time for an appeal of the action has lapsed; it does not imply the authority to revoke a vested interest, such as a 510(k) classification determination. The cases make clear that the implied authority to reconsider a matter only exists until jurisdiction lapses, *i.e.*, a decision becomes final.

For example, in *West v. Standard Oil Company*, 278 U.S. 200 (1929), the U.S. Supreme Court ruled that the Secretary of Agriculture had authority to consider a dispute about the character of contested lands, notwithstanding that the Secretary had previously ordered a dispute over the lands dismissed. The Court□s holding that the order of dismissal was not a final act hinged on two factors. First, the Court found that the dismissal did not reflect a determination on the merits following a full evaluation of the facts. *See id.* at 213. Second, and more importantly, the Court determined that the dismissal did not result in a patent, or an instrument embodying a binding determination of rights in the land. *See id.* at 219 (after issuance of an order conferring rights, administrative findings of fact relied upon in issuing the order □are conclusive, in the absence of fraud or mistake□). For these

reasons, the Court found that no final order had issued, and jurisdiction remained with the Secretary. After jurisdiction lapses, however, there is no implied agency authority to reconsider and alter a previous order. *See Prieto v. United States*, 655 F. Supp. 1187 (D.D.C. 1987) (rejecting the Department of the Interior's revocation of the trust status of certain lands because the Department had failed to issue its reconsideration within the thirty day period permitted for appeals, and its jurisdiction over the trust status of the lands therefore ceased).

Timing is critical to an agency's ability to reconsider its actions. In *Albertson v. FCC*, a case frequently cited for the principle that "the power to reconsider is inherent in the power to decide," the reconsideration fell within the 20-day period permitted for an appeal of the administrative board's initial decision. *See* 182 F.2d 397, 399 (D.C. Cir. 1950). The *Albertson* court wrote: "the power of the Commission to hear and determine matters arising under the rehearing provision . . . carries with it by implication the authority to reconsider . . . within the twenty days allowed for an appeal. . . . That is so, for within such period jurisdiction over the contested order remains with the commission." *Id.* Thus, while this decision has occasionally been cited for a broad power of an agency to reconsider its actions, *see Civil Aeronautics Bd. v. Delta Airlines, Inc.*, 367 U.S. 316, 339 (1961) (dissenting opinion), the case in fact is a restatement of the principle of *Standard Oil* that an agency may reconsider its actions, but only before passage of time or other events render the action final.

Once FDA issues its substantial equivalence order, a device's classification and marketing status are final. On the day a substantial equivalence decision is received, the product could be marketed and the review process would lapse. At this stage, the case law FDA relies upon would bar a change in the device's classification status, except through a Congressionally-mandated statutory process. At best, FDA could argue that under "517(a)(8) of the FD"C Act it has 30 days until jurisdiction would lapse to reconsider a classification decision under section 510(k)/513(f)(1) because any interested party could appeal a substantial equivalence determination. Even if one accepted this view, FDA's authority to reconsider a premarket notification classification decision would lapse after 30 days, coincidental with the expiration of the time period for an appeal.

In sum, FDA simply cannot rely on the principle of an implied power of reconsideration to authorize rescission at any time after the agency issues an order of substantial equivalence. Such a rule would be unlawful because it would effectively deny finality to any FDA order, and would be at odds with judicial authority that unequivocally states that an agency's jurisdiction to reconsider a matter ceases when an order becomes final. Although FDA could argue that a substantial equivalence order remains open until all appeal rights are extinguished, even then the agency would have only 30 days to reconsider a premarket notification classification order.

II. FDA CAN ONLY NULLIFY A FINDING OF SUBSTANTIAL EQUIVALENCE IN CASES OF FRAUD OR ADMINISTRATIVE MISTAKE OR ERROR.

As the 510(k) Working Group points out in its CDRH Preliminary Internal Evaluations Report, "agencies have inherent authority to reconsider their decisions in certain circumstances, such as where there has been fraud or error, and to rectify their mistakes." 510(k) Working Group Preliminary Report and Recommendation at 58. However, this authority does not create a basis for 510(k) rescission authority. Rather, it allows the agency to nullify substantial equivalence determinations in the rare case of fraud or administrative mistake or error.

For example, in *American Trucking Association v. Frisco Transportation Company*, 358 U.S. 133 (1958), the U.S. Supreme Court rested its ruling that an administrative agency may correct inadvertent errors in its decision-making upon a factual finding that the Interstate Commerce Commission's failure to specifically reserve authority in trucking certificates to cancel the certificates was clerical inadvertence or mistake rather than a policy change. 358 U.S. at 146. This principle would permit FDA to reconsider, without express statutory authority, any decision reflecting clerical errors, for example, were a reviewer to inadvertently omit the letter "N" before "SE." The principle does not, however, permit the agency to rescind a substantial equivalence determination on substantive grounds, for example, an agency reassessment of data or receipt of new safety and effectiveness information that put in question a prior determination. *See Concerned Citizens of Bridesburg v. EPA*, 836 F.2d 777, 786 (3d Cir. 1987) (distinguishing typographical errors from substantive agency determinations resulting in approvals).

The 510(k) Working Group cites *American Therapeutics Institute v. Sullivan*, 755 F. Supp. 1 (D.D.C. 1990), as authority that agencies can reconsider decisions in certain circumstances. The decision in *American Therapeutics Institute* is consistent with the line of cases construing a narrow administrative authority to reopen orders that may be legitimately characterized as mistakes. Specifically, the court dismissed a pharmaceutical company's case against FDA challenging the agency's summary rescission of an NDA six weeks after its issuance on grounds of inadvertence because FDA rescinded on the basis of information that existed at the time of the approval and that, if known by the reviewing official during the application's review, would have resulted in disapproval. However, the court's holding only reflects the determination that the agency's use of rescission shortly following an inadvertent error was not so clearly ultra vires as to justify its intervention in a matter properly resolved by the court of appeals, which had exclusive jurisdiction to hear appeals of NDA denials under section 505(h) of the FD"C Act. *See id.* at 2. Far from establishing a precedent permitting 510(k) rescission, the case is extremely limited and only demonstrates the reluctance of a district court to intervene in a statutorily-defined appeals scheme after determining that the case presented "an unresolved issue of statutory interpretation and administrative law within the exclusive jurisdiction of the Court of Appeals." *Id.* The district court determined it was without

jurisdiction to grant relief against the government, unless FDA's action was clearly beyond the scope of its authority, and that the court of appeals had exclusive jurisdiction to determine whether the agency's denial of an NDA was lawful.

Importantly, courts have taken strong exception to attempts by agencies to change past actions through purported corrections of mistakes based upon inadvertence or fraud as a means to legitimize changes in policy. For example, in *Prieto v. United States*, 655 F. Supp. 1187 (D.D.C. 1987), the court wrote that "perhaps the most compelling reason" of several for rejecting the attempted revocation of a trust status was the Department of Interior's pretext in relying on an unfounded assertion of fraud to "bootstrap de novo review" of its initial determination. *Prieto*, 655 F. Supp. at 1192. In another illustrative case, after reviewing a record that clearly demonstrated a policy change, the court in *Concerned Citizens of Bridesburg v. EPA*, 836 F.2d 777 (3d Cir. 1987), rejected EPA's efforts to characterize approvals of state odor provisions as "inadvertent" where the agency had relied on the approvals in several other decisions in a thirteen year period, concluding the agency's efforts to revise its approvals reflected "a clear change in policy." *Concerned Citizens of Bridesburg*, 836 F.2d at 786.

The case law provides agencies with narrow authority to reconsider and reverse previous decisions in the case of fraud or administrative mistake or error. In the 510(k) context, FDA would be allowed to nullify substantial equivalence determinations if fraud was used to obtain a substantial equivalence order, or the substantial equivalence determination reflected clerical or other administrative errors. The case law relied upon by the Working Group does not, however, permit the agency to nullify a 510(k) determination on substantive grounds.

III. RESCINDING ONE 510(K) CLEARANCE COULD RECLASSIFY AN ENTIRE GROUP OF DEVICES.

The 510(k) clearance process is a classification system based on predicate devices' classifications. Consequently, rescission of one 510(k) clearance would reclassify not only that device, but all devices that FDA determined to be substantially equivalent to it. This result would adversely affect all individuals whose rights to market such devices derive from a rescinded 510(k). In fact, the effect of a rescission on a predicate device, and all devices classified through reliance on the rescinded predicate, would be a reclassification into class III independent of the FD'C Act's reclassification authority, and a resulting PMA requirement before marketing. Permitting rescission would result in the denial of a statutory process that is intended not only to protect individual interests, but the public health.

Rescission of a 510(k) is unlike the withdrawal of a PMA, IDE, or PDP. These withdrawals are specifically authorized under the FD'C Act, and are product specific. Withdrawal of a PMA, IDE, or PDP only has direct regulatory consequences for a single product, and prior to a withdrawal becoming final, the FD'C Act prescribes protections

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for the potentially affected party. In contrast, rescission of a predicate exceeds the interest of an individual and has potentially far reaching consequences, yet is unauthorized by the FD□C Act, and therefore, without protective processes to avoid governmental error or abuse.

Several concerns flow from the principle that rescission of a 510(k) is a reclassification action. First, as described below, assuming, arguendo, the existence of rescission authority, each potentially adversely affected person must be provided with adequate notice and an opportunity to participate in the rescission process. It is not enough for FDA to engage the 510(k) holder. Second, several express reclassification authorities exist under the FD□C Act. An effort by the agency to add a new one without a statutory basis warrants close scrutiny to ensure that FDA has not deviated from the legislative intent regarding device classification. Last, close scrutiny is warranted to ensure that the agency is not trying to circumvent use of its enforcement authority through the creation of an administrative substitute without adequate procedural protections.

IV. ASSUMING AUTHORITY TO RESCIND 510(K) CLASSIFICATION DETERMINATIONS, ANY RESCISSION REGULATION WOULD BE ACCOMPANIED BY AND INCLUDE SUBSTANTIAL PROCEDURAL PROTECTIONS AND RESOURCE BURDENS FOR FDA.

The 510(k) Working Group recommends that CDRH consider the procedures that would be necessary to rescind a 510(k). As stated above, the rescission of one 510(k) clearance would adversely affect all individuals whose right to market a device is derived from the rescinded 510(k). Any agency action with binding consequences for a group of individuals requires notice to all members of the group with an opportunity for comment. This is a basic principle of administrative law, *see* 5 U.S.C. □553, and inherent in the FD□C Act□s reclassification provision for preamendment devices and devices substantially equivalent to them, *see* □513(e) (requiring notice and comment rulemaking to reclassify devices to a lower classification).

If one assumes that FDA has the authority to rescind a 510(k), notice of the basis for the agency□s rescission cannot be limited to the 510(k) holder of record. FDA□s regulations require the agency to announce administrative action □of general or particular applicability and future effect□in the Federal Register. 21 C.F.R. □□10.3(a), 10.40(b). Further, to satisfy the Administrative Procedure Act and 21 C.F.R. Part 10, the notice must provide an adequate description of the bases for the agency action to allow meaningful comment by affected parties. 5 U.S.C. □553(b); 21 C.F.R. □10.40(b)(1)(vii). Thus, legally sufficient notice and the opportunity to comment must be provided to all individuals whose marketing clearance may be invalidated by a rescission.

In addition to notice and comment rulemaking, FDA must provide adequate procedural protections for each member of the class affected by the rescission. Because a substantial equivalence order permits marketing of a device based on the device□s classification,

issuance of the order effectively creates a property right that FDA has recognized in the context of persons selling their substantial equivalence orders and access to the agency file that supported the device's classification and clearance determination. *See* FDA, CDRH, *Device Advice, Device Regulation and Guidance: Medical Devices – Premarket Notification 510(k), at* http://www.fda.gov/MedicalDevices/DeviceRegulationand Guidance/GuidanceDocuments/ucm150086.htm (stating that "a 510(k) may be bought, sold, or transferred. FDA is not involved in transfers of ownership. The new owner should maintain information documenting the transfer of ownership of a 510(k), including any legal transactions that took place, in its 510(k) files.").

Before the agency may abrogate such rights, it must provide each potentially adversely affected party with adequate process for challenging the factual basis of a revocation, as applied to that party. *See e.g., Londoner v. Denver*, 210 U.S. 373 (1908) (requiring hearings for actions affecting identifiable individuals "who were exceptionally affected, in each case upon individual grounds").

The FD"C Act is consistent in defining the procedural rights of persons facing the loss of marketing rights, e.g., device and drug approvals. Specifically, when the agency undertakes to withdraw a device's PMA, the Act requires that the agency issue notice to the affected party and an opportunity for an informal hearing to challenge the proposed withdrawal order. Thereafter, if the PMA is withdrawn, the FD"C Act provides the affected person the option of an independent advisory committee review or a formal evidentiary hearing before an administrative law judge to challenge the agency's order to withdraw a PMA. In light of the strong protections afforded in other instances of agency revocation of marketing rights, the proposal's provision of only the right to an opportunity for an informal hearing is inadequate, and arbitrary and capricious. *See, e.g.*, *Teva Pharm. USA Inc. v. FDA*, 182 F.3d 1003 (D.C. Cir. 1999) (inconsistent treatment by the agency of similar situations is arbitrary and capricious).

Important protections afforded under Part 12 of FDA's regulations include a full evidentiary hearing, the right to cross-examine witnesses, an administrative law judge, and a greater opportunity to discover the agency's case than that provided in an informal hearing. These protections are critical to the accurate resolution of factual disputes such as those that would arise in the context of a proposed 510(k) rescission. All parties whose interests would be harmed because of factual and legal conclusions reached by the agency regarding a marketed class I or II device, *i.e.*, a predicate device, must have effective opportunities to contest the facts that underlie the proposed rescission.

Further, any regulation proposed by FDA regarding 510(k) rescission would be a "significant" regulatory action under an Executive Order governing regulatory planning and review, and would require review by the Office of Management and Budget's (OMB's) Office of Information and Regulatory Affairs (OIRA). Under Executive Order number 12866, as revised by Executive Order number 13258 and Executive Order number 13422, "[f]ederal agencies should promulgate only such regulations as are

required by law, are necessary to interpret law, or are made necessary by compelling public need.□ Exec. Order No. 12866, 58 Fed. Reg. 51,735, 51,735 (Oct. 4, 1993). This Executive Order requires agencies to annually provide OMB with a regulatory plan that includes a list of significant planned regulatory actions and the legal bases for such actions (e.g., □whether any aspect of the action is required by statute or court order□) for review by OIRA. *Id.* at 51,738. OIRA circulates each agency□s regulatory plan to regulatory policy advisors, for example, the OMB Director, and other agency heads. *Id.* at 51,738-39; Exec. Order no. 13258, 67 Fed. Reg. 9385, 9385 (Feb. 28, 2002). If any planned significant regulatory action conflicts with another agency□s policy or planned actions, is inconsistent with the priorities of the President of the United States, or is not required by law, necessary to interpret law, or made necessary by compelling public need, then the Director of OMB □may consult with the hea[d] of [the] agenc[y] with respect to [its] Plans, and, in appropriate instances, request further consideration . . . .□ Exec. Order no. 12866, 58 Fed. Reg. at 51,739; Exec. Order no. 13258, 67 Fed. Reg. at 9385.

The Executive Order defines significant regulatory actions as those that, among other things, may □[h]ave an annual effect on the economy of □100 million or more or adversely affect in a material way the economy, a sector of the economy, [or] . . . public health or safety.□ Exec. Order no. 12866, 58 Fed. Reg. at 51,738. Many types of devices that reach the market by means of a substantial equivalence order result in □100 million of business or more annually for manufacturers, distributors, and others in the health sector of the economy. Compound the value of the specific device by all substantially equivalent devices that could be affected by a rescission order and, even if the agency issues only a single rescission order in a year, the potential to exceed □100 million annually is likely.

The Executive Order also defines significant regulatory actions as those that □[r]aise novel legal or policy issues arising out of legal mandates, . . . or the principles set forth in this Executive [O]rder.□ *Id.* One principle enumerated in the Executive Order is that each agency □shall avoid regulations . . . that are inconsistent, incompatible or duplicative with its other regulations . . . .□ *Id.* at 51,736. As discussed below, rescission would duplicate, although without adequate protections, many of the enforcement authorities available to FDA under the FD□C Act, and of course, the FD□C Act□s reclassification provisions. Because 510(k) rescission is not authorized by the FD□C Act, and relates to a complex classification/marketing clearance question, any FDA regulation addressing or proposing rescission would be significant.

As amended, the Executive Order requires each agency to identify the □specific market failure . . . or other specific problem that it intends to address . . . that warrant new agency action, as well as assess the significance of [the] problem, to enable assessment of whether any new regulation is warranted.□ Exec. Order no. 13422, 72 Fed. Reg. 2763, 2763 (Jan. 23, 2007). As explained below, FDA does not need to rescind 510(k)s in order to protect the public health by removing predicate devices from use. As a result,

this new agency action could not be reasonably justified under the Executive Order. In light of yet another Executive Order requirement to assess the costs and benefits of the intended regulation, and . . . propose or adopt a regulation only upon a reasoned determination that the benefits of the intended regulation justify its costs a rescission regulation should not go forward. Exec. Order no. 12866, 58 Fed. Reg. at 51,736. As discussed above, the costs of rescinding a premarket notification could be quite substantial because not only would the rescinded 510(k) device be affected, but each and every device that claimed the device as a predicate would be affected.

In sum, a regulation establishing rescission of classification determinations would require substantial and costly procedural protections and compliance with Executive Order number 12866 (as amended) that would require that the cost of a rescission regulation be justified by a benefit, assuming authority exists to promulgate and enforce such a regulation. Because inappropriate predicates can be removed from use through administrative or judicial means at considerably less expense than a rescission proceeding that could implicate numerous devices and persons, a rescission regulation could not be reasonably justified in the context of the Executive Order.

V. FDA DOES NOT NEED TO RESCIND A 510(K) CLEARANCE TO PROTECT THE PUBLIC HEALTH.

Although the FD C Act does not provide FDA with the authority to rescind 510(k)s, it does provide several other means through which the government can remove an unsafe or violative product from the market, and thus, eliminate those products as predicates in the premarket notification process. FDA does not need 510(k) rescission to protect the public health.

For example, under the FD C Act, the government has express authority to remove devices from commercial distribution and use through the Act s injunction and seizure authority upon demonstrating, by a preponderance of evidence, that a device is adulterated or misbranded, *see* 332 334. The government can also effectively remove a device from the market through its replacement authority. *See* FD C Act 518(b). Moreover, the FD C Act provides FDA with very powerful administrative remedies to protect the public health, including mandatory recall authority, *see* 518(e) (authorizing a recall of any device that presents a reasonable probability of serious, adverse health consequences or death) and the authority to promulgate a regulation to ban a device, *see* 516 (if a device intended for human use presents substantial deception or an unreasonable and substantial risk of illness or injury and the manufacturer does not comply with the agency s request to correct or eliminate the risk through labeling).[1]

[1] Removal from the market of a device by FDA, and a judicial order of misbranding or adulteration, will result in the elimination of a predicate when the action would prohibit the re-introduction of the device into commerce. In other words, devices that can be reconditioned without new 510(k)s, e.g., if a device is enjoined from a distributor because of Good Manufacturing Practice (GMP) violations, once GMP-

The agency can use its express statutory authority under the FD□C Act to obtain a court□s determination of misbranding or adulteration, or device replacement order. These outcomes would eliminate devices from being predicates, *see id.* □513(i)(2), without the need for additional authorities. In other words, if there is something violative or dangerous about a specific device, the remedy is an action against the device or device owner and not against the □type of device□classified under section 510(k).

VI. THE GROUNDS PREVIOUSLY ASSERTED BY FDA FOR RESCISSION AUTHORITY DO NOT PROVIDE LEGITIMATE BASES TO RESCIND SUBSTANTIAL EQUIVALENCE ORDERS.

In a 2001 proposed rule, FDA asserted six grounds as bases to rescind 510(k) classification orders. *See* 66 Fed. Reg. 3523, 3524-25 (Jan. 16, 2001). None of these grounds necessitate the conclusion that a substantial equivalence order should be revoked. Several of the grounds previously relied upon by FDA permit a change in classification because the agency has altered its standards for making a substantial equivalence determination for a type of device. Other grounds for rescission asserted in the agency□s 2001 proposal are deficient because, even assuming their presence, it does not follow that rescission would be the appropriate remedy. In sum, none of these justifications in 2001 or now justify rescission.

VI. CONCLUSION.

FDA does not have express or implied statutory authority to rescind 510(k) classification determinations, nor are there compelling policy grounds to do so. We agree that FDA can nullify a substantial equivalence determination, if the 510(k) submitter procured the determination through fraud, or if the agency made an inadvertent administrative mistake or error and corrected it prior to the order becoming final. Rescinding one 510(k) clearance could potentially reclassify a group of devices, and FDA does not need to take such action in order to protect the public health. The FD□C Act provides the agency with numerous efficient means to remove unsafe or violative devices from the market, and eliminate them as predicates. Moreover, the FD□C Act authorizes FDA to reclassify devices based on new information, including reassessment of past information in the administrative record. The Working Group indicated that rescission would be seldom used in response to particular circumstances; we believe the law now provides adequate remedies for any such circumstance and fully provides adequate protection of the public health if the agency is willing to use the remedies Congress gave it to ensure safe and effective devices.

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compliant, the device is no longer adulterated and therefore could be marketed without any change to the device. Section 513(i)(2) is intended to eliminate predicates when the device cannot be re-introduced into commerce under its past clearance authority, *i.e.*, when modifications to the device to make it lawful would require a 510(k).

ATTACHMENT C

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Proposal for Strengthening the 510(k) Process for a Subset of Medical Devices

The Premarket Notification 510(k) regulatory pathway ensures that diverse medical devices are appropriately regulated by creating a risk-based, science-driven classification system that *includes a comprehensive and vigorous review of device performance and test data.* A 510(k) submission for even simple devices may contain hundreds and in some cases thousands of pages of evidence demonstrating the safety and effectiveness of the device under review, including, where appropriate, clinical testing and data. By permitting incremental device improvements, today's 510(k) regulatory process is a successful and effective means to ensure the safety and effectiveness of medical technology while encouraging device development and facilitating the availability of high quality medical devices to meet the needs of the American public. Every year, approximately 3,600 new and improved devices are cleared via the 510(k) process – a remarkable record of achieving the twin goals of supporting medical innovation and providing the regulatory rigor necessary to assure that devices are safe and effective.

Challenges

Over the past two years, concerns have been raised regarding the adequacy of the 510(k) process to assure the safety and effectiveness of certain products that are cleared through the 510(k) regulatory pathway. AdvaMed believes much of this concern may arise from a lack of understanding among some stakeholders about the requirements of the 510(k) process and how it fits within the broader regulatory scheme including establishment registration and medical device listing, medical device reporting, good manufacturing practices as demonstrated by compliance with the quality system regulation, labeling requirements and provisions against adulteration and misbranding. This broad regulatory scheme assures that there is adequate FDA oversight and control throughout the medical device life-cycle.

FDA has also raised concerns, specifically regarding:

- The need for clinical information for some products when bench or animal testing are not adequate to provide assurance of safety and effectiveness or does not provide adequate understanding of the device
- The lack of access to final labeling copy prior to market introduction
- The lack of visibility to device changes that take place after marketing clearance including labeling and design changes that do not meet the criteria for a new 510(k) submission and
- The limits of postmarket controls.

More broadly, FDA has raised concerns about key aspects of reliance on predicates to determine the safety and effectiveness of new devices. For example, FDA has asked whether it is appropriate to clear a device based on the use of older predicates that no longer represent the standard of care and has raised concerns about the use of multiple or split predicates.

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Current State

For the majority of Class II devices with low and moderate risk, or whose technical and clinical performance is well characterized, the current premarket notification requirements are adequate and appropriate, and provide FDA with the necessary information to conduct its substantial equivalence review.

For other devices whose intended use has the potential for increased concern or whose technology is being used in a new application, FDA has the authority to request any data necessary to assure the product is safe and effective. FDA also has the authority to require special controls. Special controls are information specific to a particular device type beyond the basic requirement of substantial equivalence that is considered important in the review of a device. Special controls can be applied to both the data that needs to be submitted for a device to be cleared for marketing beyond the basic requirement of substantial equivalence and to requirements relating to conditions of use. Special control documents have been developed for devices such as contact lenses, influenza assays, IV sets, sutures, and diagnostic ultrasound devices and transducers.

The 510(k) system works well for most devices, but in more complex submissions there appears to be a lack of clarity and consistency in the 510(k) review process. While there is no evidence to support that this has resulted in the clearance of unsafe or ineffective products, it has been a source of frustration and delay for manufacturers, especially new and small entities, trying to provide appropriate evidence to meet FDA requirements and has contributed to public concern about the process.

PROPOSAL

To meet FDA's mission of both protecting the public health *and* advancing the public health by speeding innovations that make devices safer and more effective, and to maintain the integrity of the 510(k) program, we recommend FDA establish requirements for additional information for a subset of Class II medical devices and *in vitro* diagnostics. Under the proposal, FDA would identify the device types subject to the enhanced information requirements and publish the list of affected device types in the Federal Register for public comment.

The list of device types to which the additional requirements apply would be reviewed periodically to add new device types where appropriate. Similarly, as more experience is gained and the use of a device becomes well-established with a historical track record of safe and effective use, the device would be removed from the list

Criteria for Identification of Class II Device Subset

The following criteria are recommended for determining which Class II devices should fall into a subset that would be subject to additional submission requirements. These criteria identify devices that may present a higher level of concern associated with their intended

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use or with their use of technology in a new application. These devices clearly meet the requirements for Class II designation and do not meet the requirements for Class III.

Device types that may fall into this Class II subset could be the following:

- Permanent implants
- Life-sustaining
- Life-supporting

However, not all device types that are permanent implants, life sustaining, or life supporting would be subject to the additional submission requirements as many of these device types have a long history of safe and effective use and do not present added concern with their intended use. FDA would determine the subset of this group for which additional requirements are appropriate *based on risk management processes*. At a minimum, if the device type meets the following criteria, additional requirements would not be necessary:

- Well-characterized uses
- Well-characterized technologies
- A record of safety in clinical use or
- Up-to-date standards, guidance and/or special controls that have proven effective.

Some examples of these devices would be sutures and dental implants.

Enhanced Submission Requirements for the Class II Device Subset
510(k) submissions for Class II devices subject to the enhanced information requirements would include the following information:

- **Technical and Clinical Information Summary**
    - Technical Information
      Although bench testing and animal summary data are typically provided in a 510(k) submission, device specific testing may be appropriate for an identified device type (see Device-Specific Requirements *below*).

    - Clinical Information
      When animal and bench testing are not sufficient to provide an adequate characterization of the device, a summary of clinical information is provided. This includes relevant information about clinical experience with the device as well as experience with similar devices and the predicate device(s). Sources of clinical information may include:

        - Published and/or unpublished reports on other clinical experience of either the device in question or a justifiably comparable device

  - Results of pre- and postmarket clinical investigation(s) or other studies reported in the scientific literature of a justifiably comparable device
  - Results of pre- and postmarket clinical investigation(s) of the device

- **Labeling Elements –** Standard label information include indications for use, warnings and precautions and contra-indications.

Device-Specific Requirements – These device-specific requirements that FDA may require at its discretion for identified device types within this subset are in addition to the general enhanced submission requirements. These could include:

- Specification of additional evidence required to demonstrate safety and effectiveness, conformance to recognized standards, or other requirements related to the device types and

- A summary of manufacturing and controls information in the form of a flow chart or other simple means to establish baseline information to which subsequent 510(k) submissions and post-clearance periodic reports could be compared.

Instructions for Use at Time of Market Introduction for this Subset
Manufacturers of Class II devices subject to the enhanced information requirements would also be required to submit a copy of the device s final Instructions for Use at the time of first marketing of the device.

Post-clearance Periodic Reports for this Subset
Propose a system, that on a case by case basis, enables FDA to request at clearance, periodic reports for visibility to important changes to 510(k) baseline information and post-clearance experience after a device is marketed. Manufacturers of Class II devices subject to the enhanced information requirements *could* also provide to FDA Periodic Reports on marketed products every three years after the date of clearance that *could* include the information such as the following:

- **Design changes** [that do not meet the criteria for submission of a new 510(k)]

- **Labeling changes** [that do not meet the criteria for submission of a new 510(k)]

- **Summary of post-clearance experience** (e.g., MDRs; complaints; clinical information published within the reporting period) and

- **Update to the applicable device-specific requirements**

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AdvaMed Proposal Responds to FDA concerns and Improves the Process
The current three-tiered classification structure of FDA device and diagnostic regulation is a risk-based approach. As such, it represents a practical and effective system for regulating an industry that is both very innovative and very diverse. The proposal effectively establishes a sub-tier of regulation for a limited subset of devices subject to 510(k), which could be accomplished without necessitating a statutory change. The additional requirements for this sub-tier add both transparency and consistency to the process for FDA and manufacturers while at the same time using the existing risk-based structure to increase the level of evidence associated with a targeted set of device types.

For the relevant subset of devices, this proposal assures that FDA has adequate clinical information needed when it makes clearance decisions, and allows FDA to specify in advance what additional information is necessary and appropriate to demonstrate safety and effectiveness. It assures that FDA has a copy of final labeling at time of market introduction, provides visibility for device and labeling changes that take place after market clearance, and provides FDA with additional postmarket data without burdening FDA with unnecessary documents or data.

With regard to concerns that reliance on predicates may not provide assurance of safety and effectiveness for some devices, the proposal addresses this issue directly by establishing specific evidence requirements for those categories of devices[1] where such requirements are necessary. Issues regarding use of outdated predicates, predicate creep, and use of multiple or split predicates all become irrelevant if there are specific evidentiary requirements that must be met regardless of the relationship of the new product to a predicate. As we have noted in AdvaMed s comments to the 510(k) review process docket, AdvaMed does not believe that FDA is required to clear any product based on any predicate without data providing satisfactory assurance to FDA that the new product is safe and effective. But the use of additional submission requirements (special controls) would clarify the evidence that manufacturers need to submit to gain product clearance, provide greater consistency in decision-making, and improve public confidence in FDA s decisions.

[1] To be clear, all 510(k) submissions include comprehensive information on the testing and performance of the device under review.

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COMPARISON OF ADVAMED AND CDRH 510(k) WORKING GROUP RECOMMENDATIONS
CLASS II SUBSET

PROPOSAL/ RECOMMENDATION	ADVAMED	CDRH WORKING GROUP	COMPARISON
Identification of a new subset ("Class IIb") for which more expansive data requirements will exist	Identification of ***small, focused, and dynamic subset*** of Class II devices subject to a sub-tier of regulation for which additional submission and postclearance requirements would apply to adequately evaluate the substantial equivalence of the device	Create "Class IIb," subset of Class II devices for which enhanced clinical information, manufacturing information, and/or additional postmarket evaluation would typically be necessary to support a substantial equivalence determination	AdvaMed's proposal does not contemplate and does not agree with the creation of a new class of devices ("Class IIb"). AdvaMed's proposal refers to a more limited and dynamic subset of Class II devices.
Statutory requirements re: new subset	Limited and fits within current classification scheme; does not require statutory change	FDA claims that creation of a new Class IIb is within the scope of the current, three-tiered device classification system established by statute	FDA may not have the statutory authority to create a Class IIb without new legislation.
Breadth of subset	Implantable, life-sustaining devices, and/or life-supporting devices; NOT included IF devices have well-characterized uses and technologies; a record of safety in clinical use; or up-to-date and effective standards, guidance, and/or special controls	Implantable, life-sustaining devices, and/or life-supporting devices (greater risk than other Class II devices); IVDs	Public FDA comments suggest Class IIb contemplated is more expansive than AdvaMed's proposed subset and could include all devices for which clinical data already are required (i.e., IVDs).
Identification of devices to include in subset	• Device types with higher level of concern associated with intended use or new technology using risk management processes; • FDA to publish list in Federal Register for comment; and • Once well-established with history	Aug. 31 Webinar: • Shuren: "... the establishment of Class IIb category is a mechanism by which we're looking to otherwise downclassify Class III devices."	The types of devices contemplated for enhanced requirements are similar, but public comment indicates that FDA's list likely would be more expansive and less subject to change over time.

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PROPOSAL/ RECOMMENDATION	ADVAMED	CDRH WORKING GROUP	COMPARISON
	of safe use, remove from list	• Includes IVDs	
Enhanced premarket requirements	• Device-specific technical bench testing • Clinical data (when animal and bench are insufficient), including published and/or unpublished reports of device or closely related device • Device-specific additional evidence of safety and effectiveness • Flow chart summary of manufacturing and controls	• Clinical data (least burdensome alternatives not discussed) • Manufacturing process and design control information • Aug. 31 webinar: The Agency recommended pre-IDE meetings to establish clinical study requirements for Class IIb devices.	As compared to the Working Group, AdvaMed's proposal contemplates alternative forms of clinical data, when necessary; device-specific nonclinical testing to support safety and effectiveness; and less extensive manufacturing information.
Post-clearance requirements	Post-clearance periodic reports (case-by-case) for design changes; labeling changes; postclearance experience; other updates	• Greater authorities to require postmarket surveillance/ condition-of-clearance studies • UDI system • Regular, periodic reports of modifications made without submission of a new 510(k)	AdvaMed did not propose enhanced postmarket surveillance or "condition-of-clearance" studies.
Labeling	Submission to FDA of final instructions for use at time of market introduction.	Regular, periodic updates to labeling. Labeling updates will be screened by FDA and posted to a public database.	AdvaMed did not propose placement of final labeling in a public FDA database.
Pre-clearance inspections	Not proposed	Proposed (with the intention of withholding clearance for noncompliance with QSR if potential for serious health risk)	AdvaMed did not propose withholding clearance or pre-clearance inspections.

ProXimal Ventures
P.O. Box 255384
Sacramento, CA 95865
October 4, 2010

Comments on Docket No. FDA-2010-N-0348

Dear CDRH:

My investment firm ProXimal Ventures seeks to provide seed-stage funding to medical technology companies whose products address large markets and that can make healthcare safer, more effective, less costly, and more accessible, through technology. I am also involved as a volunteer in regional economic development efforts in support of dozens of such seed-stage companies. As a retired healthcare regulatory lawyer, I have some experience with agency-industry relations. As an American, I am concerned about our sluggish economic recovery, loss of manufacturing jobs, and the trend for early-stage medical device research and development to be sent overseas.

I have three general comments that address the FDA's role in medical device regulation that I believe would greatly enhance the ability for new innovation in medical technology to come to market where healthcare can be improved and made less costly, and where new industry can arise to rebuild our economy. Some may require statutory change, but I offer them in the spirit with which they have been solicited – in pursuit of a more effective and efficient regulatory process.

I also wish to thank Jeffrey Shuren and other FDA personnel who were at Stanford September 27-28 for their excellent program.

1. ***Small Innovative Trial Exemption.*** Persons subject to FDA medical device jurisdiction range from multi-billion dollar med tech companies, to minimally funded start-ups, researchers and inventors. Assertion of FDA jurisdiction over concept-stage and feasibility-stage prototype testing is of arguable public benefit and of such high cost that much of such early-stage testing is being driven overseas, or is dying due to lack of venture funding to support it. While it provides in theory an additional layer of protection to small patient populations, in practice it does nothing but stifle innovation. The FDA should exempt early-stage clinical trials involving fewer than (pick a number from 10 to 100) patients from FDA regulation entirely. Potential abuses and other harm to patients that might occur in such trials are adequately protected against by the professional integrity of physicians performing such testing, state licensing boards that supervise and discipline them, and by institutional review boards reviewing and approving such tests within institutions such as hospitals, plus they are by definition of very limited scale. FDA can publish whatever standards it expects to see in clinical trials that may ultimately be submitted to it in support of a PMA or "Class IIb" de novo 510(k) application, and early-stage product developers can follow these guidelines, once they've

perfected the prototypes they intend to go forward with, without having the FDA insert itself into the process of approving such trials through application for an IDE, in other than major trials. For most innovators and the angel investors who might support them, "getting FDA approval," even of just an IDE, is a major, complex and unknown process (subject to the added cloud that it is changing) that halts progress, or ends due diligence. Having an exemption for small-scale activity removes this major concern from the investment calculus. Although the data that results may not meet FDA standards, it may be sufficient to improve design, and attract the capital needed to move forward.

Justification. Such early stage innovative work hardly constitutes "interstate commerce," the potential harm is miniscule compared to the FDA's responsibilities with respect to devices being consumed in the millions or hundreds of thousands annually, and is adequately protected against at the state level and by local institutional review boards. Not having to deal with the FDA at all at the earliest stages of product development will add to efficiency in the innovation process. For every device for which clinical data is submitted to the FDA, there may be many device versions tested and improved before a final version is more fully tested, and there may be many devices or versions that are abandoned at this stage and never pursued. FDA involvement in all but those that go forward for major testing is wasted effort and an unnecessary burden on the innovators. The FDA should not seek to regulate this innovative stage. By exempting it, early-stage money will become much more available.

2. ***Adopt a Time-Limited "Provisional Approval" Process Based on Lesser Showings of Safety and Efficacy.*** FDA front-loads its regulatory burden, so that massive evidence of safety and efficacy may be required before the product can be introduced to market at all. The cost of meeting this burden can be in the neighborhood of $100 million. Yet most products that begin the route to approval never make it through to commercial success. It is now more common than not for such products to be tested in overseas markets and introduced in Europe before initiating FDA approval processes, a phenomenon almost entirely driven by regulatory burden. Venture capital funding for such new products is seriously constrained such that many promising new technologies have no way to move forward. VCs may require companies to pursue a foreign route. FDA should consider having a much lower burden in order to secure an initial "provisional approval" for a period of years, say five years, with potential one year extensions, perhaps subject to limited geographic area, such as a single state, during which time agreed-upon, more detailed clinical evidence can be compiled and published, and some degree of clinical experience independent of company-clinical trials can be generated. Perhaps limited geographic areas could also be approved, which would allow new products to prove themselves in a smaller market, while clinical dated is being accumulated.

Justification. More new products with great promise will become available in the US much earlier under provisional approval. The risk inherent in reduced initial clinical evidence required is mitigated by a limited time-frame during which provisional approval will be effective. At the time of final approval, both the Company and the FDA will have greater knowledge about clinical safety and efficacy, as well as unanticipated

developments from non-Company sponsored clinical use, to inform optimal approvals, indications for use, and conditions of use. Such reform would tend to halt the transfer of early stage design and development overseas. The amount of venture capital needed to get a new product to the stage where it can be acquired by a big company or go public will be greatly reduced, spurring greater activity. The medical community's role in filtering what devices should get used for what indications will occur on a parallel track with the agency's, rather than only after final agency action.

3. ***Redirect Limited FDA Resources from Pre-Market to Post-Market Supervision.*** The greatest harm to patients from defective medical devices occurs from high volume, implantable devices whose harmful effects become apparent only after lengthy implant experience, or from off-label use. FDA generally regulates devices after approval only due to reporting of problems, or very occasional audits. FDA should expand its supervision of post-market approval utilization of devices, to focus more of its limited resources on the areas of greatest potential harm, and reduce its focus on pre-market approval, by exempting concept-stage prototype testing, lowering initial provisional approval requirements, and negotiating post-market monitoring and supplemental clinical trial evidence requirements.

Justification. FDA's purpose is to protect the public from unsafe devices in the market, yet it functions instead as a gatekeeper to enter the market. This is similar to a police force trying to stop pickpockets in a marketplace by requiring all who would enter to prove that they are not pickpockets, while failing to assign any police to monitor the crowd. Every time a pocket gets picked, additional proof is required at the gate, stifling market activity. If instead, you put more cops in the market, and make it easier to get through the gate, you'll have a more robust yet safer market.

Very truly yours,

//s//
Cary M. Adams
Principal

1801 Rockville Pike
Suite 300
Rockville, MD 20852
Tel: +1 301 530 9222
Fax: +1 301 272 2150
www.quintiles.com

QUINTILES

October 4, 2010

Jeffrey Shuren, MD, JD
Director - Center for Devices and Radiological Health
U.S. Food and Drug Administration
10903 New Hampshire Avenue, WO66-5429
Silver Spring, MD 20993

Subject: Docket No. FDA-2010-N-0348 – Call for Public Comments

Dear Dr. Shuren:

On behalf of the Medical Device Development practice of Quintiles Consulting and our medical device clients, I am submitting these comments in response to FDA's notice in the Federal Register requesting public comment on these reports. Quintiles comments are in the attached table are limited to the "Foreword: A Message from the Center Director", and the "Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations". We fully support the proposed recommendations delineated in the "Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations".

Medical Device Development within Quintiles Consulting is regarded by many as the leading global regulatory consultancy for device development. The employees of our group have 57+ years experience as former FDA reviewers, supervisors, and managers at CDRH and 93+ years experience in device industry and/or as device consultants. Our experience extends across virtually all device types, including *in vitro* diagnostics and combination products, and across all points of the development continuum and all phases of the company life cycle, from start-up to established companies. Because of our 15+ year history with diverse device types, we have interacted with virtually every component of ODE and OIVD and thus have observed firsthand the emergence of varying practices and inconsistencies. In addition to Medical Device Development services, we provide our clients with seamless continuity supporting requirements for medical device quality systems, Good Clinical Practices, Good Laboratory Practices, and Process Optimization. We hold ourselves to extremely high standards of professionalism and are fully committed to advancement of FDA's public health mission.

Thank you for considering our comments. Quintiles Consulting remains dedicated to working with and supporting CDRH in the process of constructive change and would be pleased to provide additional clarification or information on these comments. Please feel free to contact me at 301-272-3113 or alternatively at david.west@quintiles.com.

Sincerely,

David West / PJ Meagher

David West, PhD, MPH
Vice President, Medical Device Development

Attachment I

Attachment I – Quintiles Comments on CDRH's Preliminary Internal Evaluations

Forward: a Message from the Center Director	Volume I: 510(k) Working Group, Preliminary Report and Recommendations	Quintiles Comment
Page 1 – first paragraph: ". . . to advance three key objectives of a balanced public health approach: fostering medical device innovation, enhancing regulatory predictability, and improving patient safety."	Page 4, 1.1 Overview / Findings and Recommendations, 1st paragraph – "An effective 510(k) program is predicated on three major elements . . ."	Quintiles Consulting fully supports the three key objectives as stated, but urges CDRH to reaffirm the critical role of a "least burdensome" process in achieving these three objectives. The concept of "least burdensome" is to assure that the process requires only the scientific and technical information that is necessary and sufficient to demonstrate that a new device is substantially equivalent to a predicate device with respect to intended use and technological characteristics. The intent of "least burdensome" is not to undercut adequate science or patient safety, but to balance necessity with sufficiency in the current process. It would seem that this existing provision of law is being treated by the agency with increasing ambivalence in communications with the regulated industry and in actions regarding 510(k) submissions.
Page 1 – third paragraph: "By increasing the predictability, reliability, and efficiency of our regulatory pathways, we can help provide better treatments and diagnostics to patients more quickly . . ."	No specific text in Volume I	Increasing predictability, reliability, and efficiency of regulatory pathways, alone, will not provide better treatments and diagnostics to patients more quickly, nor stimulate investment in the development of promising new technologies, if the pathways are overly burdensome. Focus should be on determining what data are necessary and sufficient so that the regulatory pathways are optimized. Again, Quintiles Consulting urges CDRH to revitalize and reinforce the intent of "least burdensome" as provided by existing law.
Page 1 – fourth paragraph: ". . . FDA recently signed an information-sharing Memorandum of Understanding with the Centers for Medicare and Medicaid Services (CMS) . . ."	No specific text in Volume I	This type of inter-agency collaboration has the potential to speed the uptake of new device technology by facilitating CMS payment decisions on new devices. However, Quintiles Consulting recommends that the coordination between the two agencies should be approached with due regard to the differences in the respective missions and statutory authorities of the agencies and with due regard for safeguarding proprietary, confidential information.

Forward: a Message from the Center Director	**Volume I: 510(k) Working Group, Preliminary Report and Recommendations**	**Quintiles Comment**
Page 1 – fifth paragraph: ". . . to address critical challenges facing the Center and our external constituencies."	No specific text in Volume I	Quintiles Consulting seeks clarification of the Center Director's charge to the 510(k) Working Group with respect to addressing critical challenges. Did the 510(k) Working Group evaluate the adherence of staff and managers to established interpretation of existing laws, regulations, and policies? If not, Quintiles Consulting recommends that this evaluation be performed before implementing 510(k) program changes because we believe that addressing discrepancies in adherence could address some, if not many, of the problems encountered by the agency and industry. If this step of evaluating adherence was considered by the 510(k) Working Group but not pursued, Quintiles Consulting seeks clarification as to the rationale of the 510(k) Working Group.
No specific text in Volume I – Center Director comments focused on higher level objectives for a balanced public health approach, page 1	Page 3, 1. Executive Summary, 2nd paragraph – "The current 510(k) program reflects the current statutory framework and FDA's implementation of that framework through regulation, guidance and administrative practice.	Quintiles Consulting recommends that FDA consider a fourth major element of the 510(k) program as acknowledging and being sensitive to the incremental innovations and changes in new devices, as well as modifications of existing devices, in comparison to the predicate devices. Additionally, Quintiles Consulting believes that the review standard should reflect commonly understood and uniformly applied interpretation of prevailing laws, regulations, and policies, as well as understanding of the role of applicable regulatory practice and appropriate precedence. Transparency should prevail whenever law, regulations, policies, practices, or precedence are put aside or otherwise not followed. And lastly, Quintiles Consulting holds that the agency should require only "necessary" and "sufficient" information for making regulatory decisions.
Section I - Fostering Medical Device Innovation - Page 2, Item 1: "Streamline the premarket pathway for lower risk novel devices"	Page 5, 1.1 Overview / Findings and Recommendations, 1st complete paragraph – "Evaluation of Automatic Class III designation"	When the 510(k) *De Novo* program was initiated as part of the agency's implementation of FDAMA '97, the pathway was efficient and timely, with agency / sponsor pre-submission meetings leading to a common understanding of the suitability of the pathway and what information was to be placed in the 510(k) and the *De Novo* petition, respectively. Expectations were set with common adherence to statutory timeframes. However in recent times, ODE has discouraged pre-submission discussions on the suitability of the *De Novo* process for a device. Moreover, various branches within ODE approach the *De Novo* process with different understandings, and have indicated in informal conversations that the statutory timeframes for *De Novo* are viewed as unimportant.

Forward: a Message from the Center Director	Volume I: 510(k) Working Group, Preliminary Report and Recommendations	Quintiles Comment
Page 2, Item 1: "Streamline the premarket pathway for lower risk novel devices", cont	Page 5, 1.1 Overview / Findings and Recommendations, 1st complete paragraph – "Evaluation of Automatic Class III designation", cont	Quintiles Consulting urges CDRH to revisit the agency practices that were in place when the program was first implemented and return to these practices, or provide clarification as to why these practices are no longer feasible. Quintiles Consulting has regrettably noted that FDA has been ambivalent in its treatment and management of the *De Novo* process. Quintiles Consulting maintains that *De Novo* process should be regarded as a legitimate pathway, when deemed appropriate by both FDA and the device company. Quintiles Consulting supports efforts to address inefficiencies in the current 510(k) *De Novo* process, as well as enhanced training of FDA personnel as to the value of this process and the value of open and earnest pre-submission discussions. The issue of requirements for clinical data should be considered independent of the issue of streamlining the *De Novo* process. Moreover, devices eligible for *De Novo*, under present statue, are devices for which there are no predicates. Thus, how could devices eligible for *De Novo* be presumed to be among certain types of devices placed in a subclass?
Page 2, Item 2: "Enhance science-based professional development for CDRH staff"	No specific text in Volume I but implicit in development of guidance and recommendations for training.	In addition to enhancing the science-based professional development for CDRH staff, Quintiles Consulting urges CDRH to include professional development with respect to existing laws, regulations, guidance, policy and practices. Oversight should not be restricted to adherence to good science, but also to adherence to applicable law, regulations, policies, practices and precedence. Thus, oversight should include holding the entire review staff (reviewers and managers) accountable for agency decision-making while adhering to good science, the law, regulations, policies, practices and precedence.

Forward: a Message from the Center Director	Volume I: 510(k) Working Group, Preliminary Report and Recommendations	Quintiles Comment
Section II – Enhancing Regulatory Predictability - Page 3, Item 4 – "Increase the predictability of 510(k) data needs by establishing a new class IIb"	Page 5, 1.1 Overview / Findings and Recommendations, 3rd complete paragraph – ". . . develop guidance to define, as a heuristic, a subset of class II devices called "class IIb" devices, for which clinical information, manufacturing information, or potentially, additional evaluation in the postmarket setting would typically be necessary . . ."	Quintiles Consulting believes that *a priori* requirements for clinical or manufacturing data will thwart innovation if not made commensurate with the degree of change of a new device from its predicate, or the degree of incremental change of a modification of an already cleared device. Rather than create a new classification, Quintiles Consulting recommends that CDRH re-examine and perhaps refine the 1986 Blue Book Memorandum guidance (#86-3) which established broad principles of when data should be required to support a 510(k), whether for a new device or for a modification of a device. Based on Quintiles Consulting experience in working with various Divisions and Branches within CDRH, we believe that some of the recent difficulties confronting the agency and the industry stem from inconsistent adherence to existing guidance. The industry encounters such inconsistencies from Branch to Branch within a Device Division, as well as across Divisions. This indicates a circumstance not driven by advanced technologies but driven by lack of CDRH training in a common philosophy and understanding of how the guidance should be applied. Quintiles Consulting firmly believes that re-consideration and revision of the 1986 guidance document, followed by CDRH-wide training, would be less disruptive for the agency and for industry than creating a new classification scheme outside the long-standing device classification paradigm established by existing statute.
	Page 6, 1.1 Overview / Findings and Recommendations, paragraph continued from page 5 – "By creating a "class IIb" device subset and making appropriate use of a streamlined de novo process, CDRH could make more predictable, timely, and consistent decisions."	The issue of requirements for clinical data should be considered independent of the issue of streamlining the *De Novo* process. Moreover, devices eligible for *De Novo*, under present statue, are devices for which there are no predicates. Thus, how could devices eligible for *De Novo*, having no predicates, be presumed to be among certain types of devices placed in a subclass?

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Page 3, Item 5 – "Notice to Industry" Letters	No specific text in Volume I	Although the existing process for guidance development may be time-consuming and to some extent cumbersome, it also provides a means for industry review and comment on draft guidance. Participation by industry and other affected constituents provides a safeguard against potentially ill-informed, impractical, or unfounded regulatory expectations being imposed on industry without adequate time for implementation or response. Quintiles Consulting agrees that a "fast track" method of providing industry with guidance would be welcomed, but recommends that the use of "Notice to Industry" letters include a feedback mechanism for industry or other affected constituents to provide comments to the agency before agency action on the guidance.
Page 4, Item 6 – "Clarify meaning of key terms in substantial equivalence . . ."	Page 4, 1.1 Overview / Findings and Recommendations, 3rd paragraph – ". . . key terms in the statutory definition of "substantial equivalence" have not been consistently interpreted by the Center . . .	Quintiles Consulting supports efforts to provide clarification and reinforce understanding of the statutory definition of "substantial equivalence" for FDA staff and for the medical device industry. Quintiles Consulting recommends FDA start this exercise from the last point in time at which the agency previously provided interpretation and guidance on defining substantial equivalence, which is FDA's Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3). Quintiles Consulting maintains that the inconsistent interpretation may be due to a lack of training and line management oversight to ensure that consistent interpretation is maintained. In our 15+ year history, Quintiles Consulting has observed that the significant inconsistencies in interpretation encountered are relatively recent phenomena. With the increasing numbers of experienced FDA employees retiring and new staff joining the agency, it would seem that these inconsistencies are more likely to be traceable to ineffective training and monitoring of training effectiveness with respect to consistent application of policy and/or guidance than due to advances in technology.

Forward: a Message from the Center Director	Volume I: 510(k) Working Group, Preliminary Report and Recommendations	Quintiles Comment
	Page 7, Item 1 Rational, Well-Defined, and Consistently Interpreted Review Standard, Same Intended Use: Lack of a Clear Distinction	"Intended Use" is a term used primarily in the context of making 510(k) regulatory decisions. "Indications for Use" or "Indications" are terms more readily recognized and understood by user healthcare professionals and patients when they appear in device labeling. Moreover, package insert labeling for drugs utilize the term "Indications and Usage", which is readily recognized by users, and is very close to the established device labeling term "Indications for Use". The agency should consider what confusion might arise among user healthcare professionals and patients who are accustomed to "Indications for Use" or "Indications". It seems that the agency should be able to address its internal problems of inconsistencies of interpretation and applying regulatory considerations for "Intended Use" though clearer guidance and better training, rather than forcing wholesale changes in terminology on itself, the industry, and users.
Page 4, Item 6 – "Clarify meaning of key terms in substantial equivalence . . .", cont	Page 7, Item 1, cont, Same Intended Use: Insufficient Guidance for 510(k) Staff and Industry	Law, regulations, and prevailing practice reflect that the product labeling and device design (explicit or implied) are established elements of a device application that should be considered in determining the "intended use" of a device. However, there is no basis in existing law or regulation to reflect that literature or existing preclinical or clinical data, in and of itself, would be a defensible basis for determining intended use. Moreover, trying to use literature or existing preclinical or clinical data as a basis for establishing intended use is likely to create potential for substantial and prolonged confusion, debate, and/or litigation.
	Page 8, Item 1, cont, Same Intended Use: Off-label Use	The approach of FDAMA '97 [Section 513(i)(1)(E)] and subsequent guidance *Determination of Intended Use for 510(k) Devices; Guidance for Industry and CDRH* Staff, January 30, 1998 (K98-1) would be a recommended starting point, perhaps with an analysis of shortcoming or limitations, if any, of that approach.
	Page 8, Item 1, cont, Different Questions of Safety and Effectiveness: Inconsistent Terminology	The 1986 guidance (#86-3) referred to "different TYPES of questions of safety and effectiveness" (emphasis added). This has served FDA and the industry well for decades and should be considered in any effort to reconcile or update the terminology and/or guidance.

Forward: a Message from the Center Director	Volume I: 510(k) Working Group, Preliminary Report and Recommendations	Quintiles Comment
No specific text in Forward	Page 5, 1.1 Overview / Findings and Recommendations, paragraph continued from page 4 – ". . . predicate comparisons . . . use of so-called "split predicates," a term that refers to using one predicate as the basis for a comparison with respect to "intended use" and another predicate as the basis for a comparison with respect to "technological characteristics" . . ..", and Page 9, Item 1, cont, Use of "Split Predicates" and "Multiple Predicates":	Quintiles Consulting believes two completely separate issues are being addressed here: (1) obsolete or ill-suited predicates and (2) "split predicates", and recommends that FDA address these issues separately. Quintiles Consulting recommends that the agency define specific criteria that would categorize a commercially available device as no longer eligible as a predicate device. When the agency deems that a particular predicate should no longer be considered as an eligible predicate device, FDA could notify manufacturers of this determination and the supporting rationale via the "Notice to Industry" mechanism or other means with timeliness of the process commensurate with public health urgency and opportunity for comment. Additionally, FDA could add a note to the 510(k) database to indicate the status as "not eligible as a predicate device", i.e., considered "misbranded". However, FDA would need to include provisions for distinguishing between a specific "misbranded" device from a more general type of device where the general type of device might remain suitable for continued commercial distribution.
No specific text in Forward	Multiple predicates / "split predicates", cont	Quintiles Consulting has understood that "split predicates" were not allowed simply on the grounds that matters of device design, performance, and labeling should be considered only within the context of the device intended use. That device design, performance, and labeling should be considered within the context of device intended use is grounded fundamentally in the law, and is reflected in numerous agency guidance documents stretching over years. Since "split predicates" were not allowed in the past, they should not be allowed now as there have been no changes to the law or guidance. If the use of "split predicates" has been allowed, Quintiles Consulting again believes this can be attributed to lack of training and managerial oversight of policy and practice. Quintiles Consulting recommends that the agency simply return to basic fundamentals of existing law and regulations in disallowing "split predicates" and also provide enhanced training of FDA personnel and industry to that effect, i.e., start with the intended use with the understanding that a new intended use creates a new device. Multiple predicates, all having a single, common intended use, should continue to be allowable to facilitate the review and marketing of innovative devices. If training is needed to clarify appropriate circumstances, then it should be undertaken.

Forward: a Message from the Center Director	Volume I: 510(k) Working Group, Preliminary Report and Recommendations	Quintiles Comment
Page 4, Item 7 – Establish a Center Science Council . . ."	Page 6, 1.1 Overview / Findings and Recommendations, 2nd complete paragraph – " . . . in part through the oversight of a new Center Science Council comprised of experienced reviewers and managers, under the direction of the Deputy Center Director for Science."	Quintiles Consulting regrets that the current circumstances within CDRH are such that the formation of a separate Center Science Council appears to be the most suitable remedy to address inconsistencies in science-based decision-making. Traditionally, CDRH line managers would be held accountable to exert a level of internal oversight which would ensure sufficient scientific rigor and conformance with medical device law, regulations and policy. In the formation of this council to assure the quality and consistency of scientific decisions, Quintiles Consulting urges CDRH to also charge this council with assuring the consistency and conformance of decision-making with existing medical device law, regulations and policies. To achieve improvements in the current 510(k) program, decision-making must be consistent from a balanced perspective of both science and regulation.
No specific text in forward	Page 6, 1.1 Overview / Findings and Recommendations, 2nd complete paragraph – ". . . recommends that CDRH develop program metrics and better systems for continuous monitoring of 510(k) program performance and effectiveness."	Oversight should not be restricted to adherence to good science, but also to adherence to applicable law, regulations, policies, practices and precedence. Thus, oversight should include holding the entire review staff (reviewers and managers) accountable for agency decision-making while adhering to good science, the law, regulations, policies, practices and precedence.

Forward: a Message from the Center Director	Volume I: 510(k) Working Group, Preliminary Report and Recommendations	Quintiles Comment
Section III – Improving Patient Safety - Page 4, Item 8 – "Require the up-front submission of more complete safety and effectiveness information to support the review of 510(k) devices"	Page 11, Item 2, cont, Quality of Submissions: Incomplete Information	Although this recommendation appears to be reasonable, in principle, it seems to extend the requirements for Class III summary and certification to all 510(k) devices, which would be to "provide a review of the risks and adverse events known and associated with the general category of devices into which the proposed device falls". Extending this requirement to all 510(k)s, which are submitted in great numbers per year, could result in workload burdens for the agency and industry. And because Class II devices frequently undergo numerous incremental changes, the value of the information is expected to be questionable and lead to frequent disagreements as to the relevance of the information to an iteration of a 510(k) device. Quintiles Consulting views this as over-reaching and believes that this requirement be limited to safety and effectiveness information immediately relevant to the device covered by the 510(k) and not to the prior versions of the device or to the claimed predicate device. For example, in FDA's "Guidance for Industry and FDA Staff - Format for Traditional and Abbreviated 510(k)s" , August 12, 2005, the agency recommends that sponsors "include a brief description of the device design requirements". This could be revised to recommend a description of device design requirements and identification of those design requirements that are essential for the safe and effective performance of the subject device. Some device-specific guidance documents recommend sponsors provide evidence of risk management activities, e.g., hazard analysis, design Failure Mode Effects Analysis (FMEA) human factors FMEA and/or process FMEA which capture safety and effectiveness issues immediately relevant to the device in question. CDRH could add this as a recommendation for all 510(k) devices.
Section III – Improving Patient Safety - Page 4, Item 8, cont	Page 11 - 12, Item 2, cont, Type and Level of Evidence Needed:	See previous comments; post-market Information: Substantial equivalence should be determined based on premarket data and analysis, and on confidence that the new device will perform as safely and as effectively as the predicate device. If the agency decides that a least burdensome approach would be to establish criteria under which substantial equivalence could be determined on a provisional basis, then the agency should provide means for safeguarding the clearances of devices found substantially equivalent to a device for which clearance is revoked for failure to fulfill "condition-of-clearance studies".

Forward: a Message from the Center Director	**Volume I: 510(k) Working Group, Preliminary Report and Recommendations**	**Quintiles Comment**
Page 5, Item 9 – "Create a searchable on-line public database to provide more detailed, up-to-date information to industry, the health care community and patients . . . one-stop source for detailed information . . . up-to-date labeling"	Page 14, Item 2, cont, 510(k) Databases:	In general, posting such information would appear to be helpful to users, patients, and the industry. However, present regulations require that 510(k)s include proposed labeling for the purpose of FDA determining the intended use of the device. Existing guidance allows for some changes to labeling without the need for submitting new 510(k)s, specifically FDA's "Deciding When to Submit a 510(k) for a Change to an Existing Device", January 10, 1997. Thus, any mechanism for posting "up-to-date device labeling" is expected to be overly burdensome for industry and FDA. An alternative would be to require manufacturers to post up-to-date labeling on their respective web sites, in which case it is publically available to users, patients, industry and the FDA. Limited Information on Current 510(k) Ownership: This used to be done, as a matter of custom, through "add to file" letters. Then FDA discouraged the practice and explained that the agency had no need or use for information on change of ownership. This raises the question of why the agency now believes it needs information on the change of ownership.
Page 5, Item 10 – "Clarify FDA's rescission authority . . ."	Page 8, Item 1, cont, Concerns about Predicate Quality and Rescission Authority	Quintiles Consulting appreciates the value of this recommendation. To be workable, Quintiles Consulting recommends that the regulation also must address how the rescinding of a 510(k) clearance would impact devices already cleared for marketing based on substantial equivalence to the device subject to the rescission. In other words, do the circumstances warranting the rescinding of a device apply equally to all devices found equivalent to the rescinded device before the rescinding action is taken? If this is the case, Quintiles Consulting urges the agency to consider how "due process" be assured for all parties. Perhaps CDRH should have a regulatory means, with timeliness of the process commensurate with public health urgency and opportunity for comment, to declare certain devices out of current clinical favor to be declared "misbranded" and thus not eligible for serving as a predicate. However, there should be provisions for distinguishing a specific "misbranded' device from a more general type of device where members of the general type of device might remain suitable for continued marketing.

Forward: a Message from the Center Director	Volume I: 510(k) Working Group, Preliminary Report and Recommendations	Quintiles Comment
No specific text in Forward	Page 10, Item 2 - Well-Informed Decision Making, Unreported Device Modifications	Revise guidance to clarify which modifications are allowable; this seems reasonable. It seems reasonable that the agency should have updated information. However, such updated information should already be available for agency review in design history files at company sites. If there is a requirement for periodic updates to be sent to CDRH, this will impose additional submission requirements on industry and obligate reviewers to review additional information not directly related to premarket review responsibilities. Review of the 510(k) "updates" is likely to fall to low review priority, similar to low review priority given from time to time for PMA annual reports and IDE annual reports If relegation to low priority occurs, the increased burden on both industry and the agency is not likely to yield the intended benefit. As an alternative, consideration should be given to issuing a guidance document on how updated information should be organized in design history files to facilitate review during routine or for-cause establishment inspections. If additional resources are available to FDA for a "510(k) update review responsibility", they could be more effectively placed in the field to undertake more frequent inspections (approaching biannual) focused on Design Controls, rather than at CDRH where they are likely to be siphoned off for uses other than reviewing routine 510(k) updates.

Forward: a Message from the Center Director	Volume I: 510(k) Working Group, Preliminary Report and Recommendations	Quintiles Comment
No specific text in Forward	Page 10 - 11, Item 2, cont, Quality of Submissions: Lack of Clarity	This proposal fails to recognize the critical interface between Design Controls and any premarket submission. Source data for product submissions such as rationales and supporting evidence should already be available in some form or another in design control documentation for the device. This should be true because FDA's Quality System Regulation, 21 CHR Part 820 requires it. A rigorous design control program should lead to ready identification of the necessary and sufficient information to fully support device safety and effectiveness or substantial equivalence. SMDA '90 authorized FDA jurisdiction over product development activities as a response to a high incident of design-related recalls. Title 21 Part 820.30 Design Controls has been in force since 1996 (the agency exercised enforcement discretion until 1997). However, inspections of medical device manufacturers do not routinely include the Design Control element, and in fact, FDA officials from ORA have publicly stated that FDA investigators tend to select other quality system elements to inspect with which they are more familiar. Thus, consideration should be given to a balance of oversight in requiring inspection of Design Controls on a routine basis and also providing guidance on how existing design control documentation should be compiled for a 510(k) submission. Introducing yet another new methodology such as an "assurance case" approach when there are two existing approaches where industry, reviewers and FDA investigators could benefit from re-training, would greatly improve the quality of documentation submitted, and also reduce duplication of effort. Such training should foster more ready agreements between agency reviewers and submitters on the design control documentation, as well as the necessary and sufficient subset of design control information to support marketing submissions. The authority to request photographs and/or diagrams, etc. already exist at 21 CFR 807.87 (e). The agency should simply inform the industry of its expectations. Such a requirement implies a requirement that a finished device be available prior to submitting a 510(k), which is not presently a requirement under existing law, Part 807, or Part 820. Moreover, a reviewer's visual inspection of a device ... as a basis for a regulatory decision ... might confound and prolong the writing of the agency record to support its regulatory decision.