regarding situations requiring the submission of manufacturing information as part of its "class IIb" guidance, and (8) pre-clearance inspection as part of class IIb – clarify authority related to statutory provision.

Subdividing class II into a "class IIa" and "class IIb," essentially creates a four-class system, which exceeds FDA's current statutory authority. We do, however, support efforts to identify a small, focused subset of some permanent implantable, life-sustaining, and/or life-supporting class II devices, which present greater risks than other class II device types, for which additional controls may be appropriate to support a determination of substantial equivalence. This subset would not include devices with well-characterized uses and technologies, a record of safety in clinical use, or up-to-date and effective guidance and/or special controls. These additional controls (e.g., clinical or manufacturing information) should be appropriate for the identified risk, but should not be applied as overarching controls to the entire focused subset. The process should include a mechanism for removing a device from the subset as more knowledge is gained. Public notice and comment should be used to identify devices within the subset, as well as for determining which of the controls would apply to the particular device type.

We note in the webinar, "FDA Discussion on the Draft 510(k) and Use of Science in Regulatory Decision Making Reports" on August 31, 2010 in discussing the types of devices that might fall into this class IIb category, CDRH cited as examples devices currently requiring clinical data, and noted this would provide increased transparency to industry regarding the types of devices requiring clinical data. While we support increased transparency to industry by providing the device types which have included clinical data in the 510(k) submissions, we note that a large portion of these devices are IVDs that would not necessarily fall into the category of presenting greater risks than other class II device types as described in the report.

For certain product areas, such as IVDs, the submission of performance data through the use of clinical specimens is not necessarily tied to presenting greater risks than other class II device types. As noted in the report "nearly all 510(k)s for in vitro diagnostic devices include information obtained by analyzing clinical samples[9]" We do not support the statements made during the webinar that any device currently evaluated with clinical data would automatically fall in this high risk subset, and thus subject these devices to additional controls as contemplated by the report.

While providing greater transparency to those device types where 510(k) submissions have contained clinical data is a laudable goal, publishing a list of these device types, for example, is more effective than designating them all as high risk and adding additional evidentiary requirements, as contemplated in the 510(k) Report for the described class IIb category.

<u>Clinical data</u>

Additional clarity regarding the use and role of clinical data in supporting determinations of substantial equivalence would be beneficial. Any such clarity, regardless of method, guidance or regulation, for example, should be subject to public notice and comment. It should also include examples of clinical data that may be used to support determinations of substantial equivalence, such as published or unpublished reports on other clinical

[9] CDRH 510(k) Working Group Preliminary Report and Recommendations at 77 footnote 165.

experience of the device in question or a justifiably comparable device, results of pre and postmarket clinical investigations or other studies reported in the scientific literature of justifiably comparable devices.

Postmarket surveillance as a condition of clearance

Under existing authority, FDA may require postmarket surveillance as a special control, (FD&C Act § 513(a)(1)(B)). FDA may also require postmarket surveillance under § 522 of the Act for certain class II devices. Furthermore, § 522 of the Act provides the authority to require certain studies related to pediatric use as a condition of clearance. For these reasons, we believe pursuing additional authority for postmarket surveillance as a condition of clearance across the board is unnecessary at this time and may lead to a proliferation of postmarket studies without corresponding public health benefit.

UDI

Abbott 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 time frame. 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 believe it is premature, at this time, to explore how data collected or associated with UDI may be used as part of the 510(k) process, and recommend CDRH defer evaluation of this option until such time as UDI is effective.

Manufacturing information

Submission of manufacturing information in the context of devices within the small, focused subset of class II devices presenting a higher risk may be appropriate when such information is needed for evaluating substantial equivalence, such as manufacturing information with respect to a unique process that is critical to the safety or effectiveness of the device. Additional guidance, subject to notice and comment, to add clarity to this specific area is appropriate.

Pre-clearance inspection

We do not support a requirement of a pre-clearance inspection as a condition of clearance for devices subject to 510(k) notification.

According to the legislative history, Section 513(f)(5) of the FD&C Act[10] was intended to address "a concern that FDA was inappropriately using the device premarket notification process for compliance purposes and not solely for its intended purpose of classifying devices intended for introduction into interstate commerce."[11] As described, device classification determinations of substantial equivalence were withheld, as firms were placed on the "reference list" under a belief that the firms were not in compliance with good manufacturing practices. As noted in the legislative history, to withhold substantial

[10] Section 513(f)(5) states, "The secretary may not withhold a determination of the initial classification of a device under paragraph (1) because of a failure to comply with any provision of this Act, unrelated to a substantial equivalence decision, including a finding that the facility in which the device is manufactured is not in compliance with good manufacturing requirements as set forth in the regulations of the Secretary under section 520(f) (other than a finding that there is a substantial likelihood that the failure to comply with the such regulations will potentially present a serious risk to health).

[11] S. Rep. No. 105-43 at 29 (1997)

equivalence determinations is inconsistent with the purpose of classifying devices and also the Act provides the agency with other substantial authority to address compliance issues.[12]

Should CDRH moved forward with this recommendation to clarify when it is appropriate to use its authority under 513(f)(5), a necessary step is providing an ample opportunity for public notice and comment.

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.

Specific recommendations pertaining to product codes: (1) develop guidance and SOPs on the development and assignment of product codes to standardize these processes and (2) enhance existing staff training on the development and assignment of product codes.

We support improvements to the product code process, including the development of guidance and standard operating procedures (SOPs) and enhanced staff training. Transparency to stakeholders of the process and assignment of product codes is also recommended, as well as industry training with respect to the meaning, assignment, and use of product codes to identify suitable predicate devices. We also suggest establishing a mechanism to allow individuals to receive notification of the development of new products.

Specific recommendations pertaining to 510(k) databases: (1) develop publicly available, easily searchable database that includes for each device a verified 510(k) summary, photographs and schematics, information showing how cleared 510(k)s relate to each other and identify the premarket submission that provided the original data or validation for a particular product type, (2) guidance and SOPs for 510(k) summaries, (3) consider standardized electronic template for 510(k) summaries, (4) clarify statutory listing requirement for the submission of labeling, (5) explore the feasibility of requiring manufacturers to electronically submit final labeling by the time of clearance or within a reasonable time after clearance and provide regular, periodic updates, and (6) guidance and regulations regarding appropriate documentation of transfers of 510(k) ownership, and update 510(k) database in a timely manner.

<u>Publicly available database and 510(k) summaries</u>
We agree with development of a 510(k) summary template and additional guidance to improve 510(k) summaries, as well as verification prior to posting.

Publication of general device photographs or block drawings, such as those publicly available in product labeling or promotional materials is appropriate post-clearance. However, we are concerned with the publication of detailed photographs or schematics. Detailed photographs or schematics are generally proprietary or confidential in nature. Due to concerns, such as reverse engineering, we believe CDRH should ensure that any process that involves the submission to the agency of detailed photographs or

[12] S. Rep. No. 105-43 at 29 (1997)

schematics is approached in a manner that does not compromise the competitiveness of the U.S. medical device industry, especially where public publication of detailed photographs or schematics will result in competitive harm to medical device companies.[13]

Without additional detail as to how the agency would show the relationship of cleared 510(k)s to one another and the identification of the premarket submissions that provided the original data or validation for a particular product type, it is difficult to offer comments on this point. Publication of this type of information must be done in a manner that does not compromise confidential or proprietary information. Additionally, provided this can be done in manner that does not compromise confidential or proprietary information, we recommend the agency consider the feasibility and resources associated with implementing this recommendation retroactively, and whether prospective implementation would be more feasible.

Clarify statutory listing requirements for submission of labeling

Prior to modifying current regulation, we recommend the agency explore the historical rationale for implementing the regulation in its current form. If such a proposal is adopted, it is unclear how the agency will manage the volume of labeling submissions it would regularly receive. More importantly, there is no public health benefit that will be gained beyond the current regulatory provision in which owners or operators are to be prepared to submit labeling upon specific request[14]. We also recommend the agency consider the number of circumstances and situations, in which it has exercised specific requests for labeling throughout the many years this regulatory provision has been in effect before moving to modify existing regulation. Because of the long-standing history of the current regulation changes in this program should not be proposed in the absence of a clear demonstration that the changes will improve public health and that such changes are administratively feasible. Due to the significant regulatory burden, any modification to the current regulations should be subject to public notice and comment.

Electronic labeling repository

We note that FDAMA provided medical device manufacturers with the ability to provide prescription device labeling in electronic format, and that as a result many manufacturers provide electronic versions of their product labeling, primarily instructions for use or package inserts, on their company websites. Establishment of a central electronic labeling repository managed by FDA for all medical devices is a significant undertaking and should be approached in a thoughtful, considerate manner.

Further, based on experience with the adoption of drug labeling into the Structured Product Labeling (SPL) format, establishment of an electronic labeling repository will be resource-intensive for both FDA and industry. It will require considerable time and resources for the manufacturer to translate labeling, if a format is specified, and to develop a tightly controlled version control system in order to ensure that labeling

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[13] As identified in the *Report to the President on the National Export Initiative: The Export Promotion Cabinet's Plan for Doubling U.S. Exports in Five Years*, "[t]here are certain sectors in which the United States often leads global technology development and innovation, such as renewable energy; civil nuclear power, smart grid, and advanced vehicle technologies; healthcare technology, biotechnology, and ***medical devices***; and agricultural production" [emphasis added] (report issued September 2010).

[14] 21 CFR 80731(e)

changes are coordinated. In addition, FDA will need to devote additional resources to ensure the labeling on the FDA website matches that of the currently marketed product in order to avoid errors and confusion for database users. Based on these considerations, we recommend the agency approach this topic methodically, allow for extensive dialogue with device manufacturers, and provide public notice and comment on any proposals.

Transfers of 510(k) ownership

We support establishing a process for documenting 510(k) transfer of ownership. FDA should establish a simple and clear process for notification of 510(k) transfer of ownership, such as a simple form requiring 510(k) application number, prior owner information, new owner information, and effective date of transfer. The process should include FDA confirmation to the new and prior owner that notification was received and a timely update to FDA's 510(k) database, and other databases, as appropriate.

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.

Specific recommendations pertaining to reviewer expertise and experience: (1) 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 and (2) establish a Center Science Council comprised of experienced reviewers and managers under the direction of the Deputy Center Director for Science to facilitate knowledge-sharing across review branches, divisions, and offices.

We support the agency's efforts 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, and offer the following suggestions:

- concerted efforts to become more involved with scientific professional societies (e.g., American Diabetes Society, Endocrinology Society) and utilization of offered training,
- increased use of vendor days and site visits, and
- consider establishing relationships with academic universities to sponsor access to technology training, to include device development and manufacturing in a continuing education program; where the university by engaging with industry would host activities.

We support the establishment of a Center Science Council comprised of 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.

Use of the Council to empower the scientific programs administered by CDRH can provide consistency across the Center, assure integrity of the programs, and facilitate timely dissemination of scientific information. Involvement in routine decisions may have the unfortunate affect of undermining the programs and value the Council can provide. The Council should rarely be used for review of product-specific decisions or other product administrative actions. For the rare occasions, in which it is used for this purpose the Center should follow a clearly defined process that has been issued with an opportunity for public comment prior to its initial use.

This process for managing new scientific information should not be used to make recommendations applicable to individual devices without input from the person with legal authority to market the device, and it should not be used in place of any legally required processes. The Council's role in any product-specific matter should be rare and it should always be advisory in nature. The substantive standards for product review should not be altered by the Council.

Recommendation: CDRH should enhance its systems and program metrics to support continuous quality assurance.

Specific recommendations pertain to: (1) develop metrics to continuously assess the quality, consistency, and effectiveness of the 510(k) programs, and also to measure the effect of any actions taken to improve the program and (2) periodically audit 510(k) review decisions to assess adequacy, accuracy, and consistency under the auspice of the Center Science Council, which would oversee communication of lessons learned and potential follow-up action.

We agree with the development of metrics as described, and recommend the agency identify metrics to assess the effectiveness of the recommendations it proposes to implement following the close of the report comment period. Developed metrics and results should be publicly available.

The implementation of periodic audits with the intent to drive greater knowledge and consistency among reviewers can improve the 510(k) program, if implemented in a manner that does not result in second-guessing of earlier decisions. Clearly defined objective audit criteria made publicly available will aid in the usefulness of the process. 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. Finally, the agency needs to ensure that these audits do not lead to revisiting previous 510(k) decisions.

Volume II: Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations

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.

Specific recommendations pertaining to premarket review: (1) clearly and consistently communicate CDRH's interpretation of least burdensome through

revision of the 2002 least burdensome guidance, (2) improve the quality of the design and performance of clinical trials used to support premarket approval applications (PMAs) through development of guidance, establishing an internal team of clinical trial experts as a subset of the Center Science Council, continued engagement in the development of consensus standards, and consider expanding efforts to include clinical trials that support 510(k)s, (3) characterize the root cause of challenges and trends in IDE decision-making, including evaluating the quality of pre-submission interactions with industry and taking steps to enhance these interactions, and (4) consider developing guidance on pre-submission interactions between industry and CDRH to supplement existing guidance.

Least burdensome

Education and training of industry and staff on the substance and application of the least burdensome principles are appropriate steps. As noted in the report, the background of FDA's 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 premarket submissions.[15]" The report further notes, "[t]hese principles are consistent with good governance in general.[16]" 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. This approach should be implemented and evaluated before any changes in current guidance are proposed.

Clinical trials

Additional guidance on FDA's expectations for clinical trial design would be helpful. The adoption of international, harmonized consensus standards, such as ISO 14155 should also be considered. Any guidance should be subject to notice and comment with an appropriate transition period for submissions under review.

CDRH should clearly outline the intended scope of the roles and responsibilities of the team of internal experts, so it does not evolve into a "review board" for each clinical trial, as this could dramatically slow down the process and ultimately slow down patient access to important, new technology. It will also be important to include expert representation from the relevant review branch of CDRH because these individuals will be knowledgeable of evidentiary expectations for a particular type of device or technology. This will help ensure that appropriate trial designs are generated and the recommendations from the internal experts provide consistent feedback to industry engaged with a particular CDRH branch. The role of the internal experts should be advisory in nature, and not alter the substantive standards for product review.

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[15] CDRH Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations at 18.
[16] Id.

Characterize the root cause of challenges and trends in IDE decision-making
Characterizing the root cause of challenges and trends in IDE decision-making is an important step in improving the process and enhancing patient access to important, new technology. This examination should also address expectations for bench testing requirements, as the release of additional guidance and lack of clear direction to IDE sponsors have put long-standing expectations in regard to bench testing in question and expectations are not always clear to IDE sponsors.

Pre-submission guidance
Additional guidance on pre-submission meetings would be helpful. It is important for industry and CDRH to work collaboratively to define acceptable testing matrixes during these meetings without having additional testing requirements raised later in the review process. To expedite development of guidance in this area we recommend the agency consider the proposed draft guidance on this topic submitted by AdvaMed in April 2008.

Specific recommendations pertaining to review workload: (1) create a standardized mechanism to rapidly assemble an ad hoc team of experienced review staff to assist with time-critical work and (2) assess and characterize challenges in reviewing IDEs within mandatory 30-day timeframe and develop mitigation steps

This appears helpful and can be a feasible mechanism to dealing with surges in workload. However, it would also be important to include expert representatives from the relevant reviewing branch because these individuals will be knowledgeable in evidentiary expectations for a particular type of technology. This would help ensure that product reviews result in consistent requirements to industry engaged with a particular branch in CDRH.

Redeployment of reviewers on an *ad hoc* basis carries the risk of increasing review times for those products whose coverage would be reduced as a result of reassignments. We recommend that a process be established to ensure that redeployments are done with full awareness of the impact on medical devices under review in branches that could lose reviewer capacity.

Assessing and characterizing the challenges in reviewing IDEs within the mandatory 30-day time fame and the development of mitigation steps for implementation during the pre-IDE process has obvious benefit to FDA and other stakeholders. The IDE regulation, 21 CFR § 812 states, in the section on Scope: "The purpose of this part is to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose." It is vitally important to maintain this objective, which fosters innovation and valuable insights from clinical investigators. An essential element of this philosophy is timeliness to ensure that the design and development of novel technologies is not delayed by protracted reviews of well-supported IDE submissions.

Specific recommendation pertaining to postmarket oversight: (1) develop better data sources, methods, and tools for collecting and analyzing meaningful postmarket information and engage stakeholders in the process, (2) conduct a

gap analysis and a survey of existing U.S. and international data sources to address identified gaps, and (3) invite stakeholders to voluntarily provide data about marketed devices to supplement CDRH's current knowledge.

To achieve this goal the UDI and other systems must be established and implemented. Data management systems must be compatible and up-to-date and duplicative efforts must be avoided. Additional detail, steps, and the agency's proposed plan for moving forward are needed to adequately comment on these activities. Should the agency move forward with this recommendation, it should provide adequate and regular opportunity for dialogue with stakeholders, including industry, to understand the scope and impact.

Recommendation: CDRH should take steps, with existing resources, to address staffing needs and enhance processes and systems that support Center-wide integrations.

Specific recommendations pertain to: (1) conduct an assessment of staffing needs to accomplish mission-critical functions, (2) determine staff needed to accommodate anticipated future scientific challenges, (3) enhance employee training and professional development for optimal staff performance, (4) consider making greater use of site visits and other means of engagement with outside experts in a variety of areas, including clinical care, (5) develop more effective mechanisms for cataloging CDRH'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 device or group of devices to Center staff.

In assessing needs, we believe it is first necessary to identify mission-critical functions, and provide an opportunity for notice and comment on these findings. We recommend the agency implement significant changes in staffing in a transparent manner.

As noted in previous responses, we agree there is merit in increased use of site visits and vendor days to enhance training.

Recommendation: CDRH should improve its mechanisms for leveraging external scientific expertise.

Specific recommendations pertain to: (1) develop a web-based network of external experts, using social media to leverage external expertise related to novel technologies and scientific questions and (2) 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 potential bias, and (3) explore site visits, including clinical care, interaction at the employee level, and collaborative relationships with other science-led organizations.

Development of standard business processes is needed, as well as a transparent understanding of the utilization of experts. Processes should include the appropriate steps to ensure that proprietary or confidential material is not compromised.

As previously noted, we support the agency's efforts 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, and offer the following suggestions:

- concerted efforts to become more involved with scientific professional societies (e.g., American Diabetes Society, Endocrinology Society) and utilized offered training,
- increased use of vendor days and site visits, and
- consider establishing relationships with academic universities to sponsor access to technology training, to include device development and manufacturing in a continuing education program; where the university by engaging with industry would host activities.

2. Applying a Predictable Approach to Determine the Appropriate Response to New Science

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.

Specific recommendations pertain to: (1) develop and implement a business process for responding to new scientific information aligned with a conceptual framework of four basic steps: (a) detection of new scientific information, (b) escalation of that information for broader discussion with others, (c) collaborative deliberation about how to respond, and (d) action commensurate to the circumstance and (2) CDRH enhance its data sources, methods, and capabilities to support evidence synthesis and quantitative decision making as a long term goal.

A prospective, standard process and metrics for new scientific information would be helpful. FDA's process should be fully transparent, and define key terms, such as "scientific information." It is important for the agency to provide for public review and comment the agency's formal proposal (process and standard operating procedure) for the detection and escalation of new scientific information that could have a bearing on determinations of safety and effectiveness.

Of the four basic steps, described in the task force report, we recommend the "deliberation" and "determining action" steps include manufacturers of the products involved when "action" affects distributed products or products under review Including industry in these activities will maximize the effectiveness and appropriateness of any actions determined to be appropriate.

Additionally, the task force report describes the factors to consider during the "deliberation" step.[17] We recommend two additional factors for consideration during the "deliberation" step. First, we recommend considering the risk/benefit profile at the time

[17] CDRH Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations at 30.

of product approval/clearance. For example, a product may be approved or cleared with acceptance of a certain understanding of risk because the benefit outweighs the risk. Assessment of "new information" at a later date should take into account the risk/benefit profile accepted at the time of approval/clearance. A shifting standard of risk/benefit assessment as "new information" becomes available can confound the "deliberation" and subsequent "determining action" step. Second, we recommend the "deliberation" step include, where appropriate, the healthcare environment in which the product is used.

Lastly, we agree the recommendation for enhanced data sources, methods, and capabilities to support evidence synthesis and quantitative decision making would be helpful.

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.

Specific recommendations pertain to: (1) streamline process for developing guidance documents and regulations, such as explore greater use of the "Level 1-Immediately in Effect" option for guidance documents, (2) CDRH should also encourage industry and other constituencies to submit proposed guidance documents, which could help CDRH develop agency guidance more quickly, (3) establish a standard practice of sending open "Notice to Industry" letters to all manufacturers of a particular group of devices for which CDRH has changed its regulatory expectations on the basis of new scientific information, and (4) take steps to improve medical device labeling and develop an online labeling repository to allow the public easy access to this information, including the possibility of posting up-to-date labeling for 510(k) devices online.

We agree with the task force that a more rapid communication mechanism is needed to convey CDRH current thinking and expectations.

Guidance

We support the development of additional product specific guidance and training for FDA staff and industry. Increased issuance of Level 1 guidance immediately in effect raises concerns about implementation of new expectations without adequate notice to affected stakeholders, which is a challenge for product and submission development. At any one time, 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. There is a real need for notice and comment on guidance documents, and therefore the use of Level 1 guidance immediately in effect is best reserved to only those places where there is an immediate public health issue.

Additionally, there should be real engagement with stakeholders in the development of guidance. For example, FDA staff participation on joint teams with stakeholders, including industry and clinicians, in the development of first drafts of guidance. Further, to maximize the value and efficiency of the acceptance of stakeholder input into the guidance development process, we recommend the agency more clearly indicate those guidance document topics in which receipt of early draft versions will enhance and expedite the development process versus those areas in which the agency is further

along in developing a draft guidance document. When documents are submitted from stakeholders there should be a feedback process as to what is being done with the proposal to increase the transparency of the process.

Notice to the Industry

We support the agency's recommendation to establish a standard practice, subject to notice and comment, for Notice to Industry letters (NTI) for use in conveying information for which CDRH has changed its regulatory expectations on the basis of new science.

We recommend the agency clearly define in a transparent manner 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 on a one to one basis. Overuse of NTIs to communicate procedural topics, such as application format, or other topics which can be addressed via Level 2 guidance will minimize 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 proposal is recognition that at any one time when 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 dynamics it is important that the NTI standard practice include a mechanism for phasing in the new expectations. As with 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 topic. Thus, a company may be able to address the subject of the NTI in another manner, and the standard practice for NTIs should continue to allow for this.

In addition to opening a docket along with the issuance of the NTI, we recommend the agency consider a establishing a timeframe for reviewing comments submitted to the docket. Additionally, following issuance of the NTI the agency should work to incorporate the new information into draft guidance for review and comment.

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. In addition, we encourage the agency to use additional communication tools to industry, so that companies contemplating the design, development and commercialization of a particular class of devices have knowledge of 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 science 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. We recommend constructing the web page in a manner that is readily accessible, consolidates all new science information in one location, and minimizes the use of multiple links to obtain this information.

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 pre-IDE meetings 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 meeting with an understanding of a path forward, only to receive a NTI shortly after the meeting. Steps to avoid such situations will benefit the agency and its stakeholders.

Electronic labeling repository

We note that FDAMA provided medical device manufacturers with the ability to provide prescription device labeling in electronic format, and that as a result many manufacturers provide electronic versions of their product labeling, primarily instructions for use or package inserts, on their company websites. Establishment of a central electronic labeling repository managed by FDA for all medical devices is a significant undertaking and should be approached in a thoughtful and considerate manner.

Further, based on experience with the adoption of drug labeling into the Structured Product Labeling (SPL) format, establishment of an electronic labeling repository will be resource-intensive for both FDA and industry. It will require considerable time and resources for the manufacturer to translate labeling, if a format is specified, and to develop a tightly controlled version control system in order to ensure that labeling changes are coordinated. In addition, FDA will need to devote additional resources to ensure the labeling on the FDA website matches that of the currently marketed product in order to avoid errors and confusion for database users. Based on these considerations, we recommend the agency approach this topic methodically, include extensive dialogue with device manufacturers, and provide public notice and comment on any proposals.

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.

Specific recommendations pertain to: (1) develop and make public a Standard Operating Procedure (SOP) that describes the process CDRH will take to determine the appropriate response to new scientific information, including expectations when a decision is made to take a particular action and clear, prompt communication to all affected parties, (2) CDRH leadership should take steps to make sure all employees have an accurate understanding of what information they are permitted to discuss with manufacturers, so that clarifying information is not needlessly withheld, and (3) CDRH should move to release summaries of ODE premarket review decisions and make public the results of post-approval and Section 522 studies that CDRH may legally disclose to provide stakeholders with greater insight into the data that guide CDRH's decisions and evolving thinking.

We agree these activities should be governed with a standard procedure that is publicly available. For cleared devices, we support the release of ODE premarket review decisions, provided appropriate procedures are in place to prevent the release of trade secrets and proprietary or confidential information. We support making publicly available the results of post-approval and Section 522 studies that CDRH may legally disclose.

In conclusion, as CDRH decides upon the items it will implement and further develops details associated with implementation, it will be essential to provide stakeholders with a meaningful opportunity for public notice and comment on the specific proposals. This is an important element of the process given the far reaching implications of many of these proposals.

Should you have any questions, please contact me at (847) 937-8197 or via e-mail at april.veoukas@abbott.com.

Sincerely,

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JIRA

e-mail : tokugawa@jira-net.or.jp

Thank you for your kind consideration about our association and having given us the opportunity of public comment on this matter.

Japan Industries Association of Radiological Systems (JIRA) hereby comments about 510(k) by the comment request [FDA-2010-N-0348].

JIRA is an international trade association representing all major global manufacturers of diagnostic imaging and radiation therapy devices in Japan. Collectively JIRA organizations represent more than 95% of the Japanese sales of those.

JIRA's opinion is described briefly as follows.

1) About the new establishment of class IIb

【VOLUME Ⅰ, page 5/119, 1.1. Overview of Findings and Recommendations】
What is meant by the text is as follows.
".....CDRH explore the possibility of developing guidance to define, as a heuristic, a subset of class II devices called “class IIb” devices,…..
Delineating between 'class IIa' and 'class IIb' would not reconfigure the current, the three-tired device classification system. ….. potential candidates for this device subset may include implantable devices, life-threatening devices, and life-supporting devices, ….."

JIRA's comment is as follows.
For other kinds of devices, the applicable guideline are not clearly described. Accordingly, clarify the applicable guideline. Particularly, diagnostic imaging devices do not contact the human body, and they are low-invasive devices. Therefore, state clearly that the diagnostic imaging devices are exempt.

2) About minor modifications

【VOLUME Ⅰ, page 69/119, 5.2.1.1. Unreported Device Modifications】
The text says in part as follows.
".....the feasibility of requiring each manufacturer to provide regular, periodic updates to the Center listing any modifications made to its device without submission of a new 510(k)….."

JIRA's comment is as follows.
Minor modifications like these should be verified essentially as design change control, when appropriate design control is carried out under a quality management system. Accordingly, it is redundant to provide regular, periodic updates. Therefore, delete it.

3) Submission of a summary of scientific information regarding

the safety and/or effectiveness

【FOREWORD, page 4/5, III Improving Patient Safety, item 8】
The Foreword says in part as follows (see the first sentence in item 8).
"…..the 510(k) Working Group recommends that CDRH consider revising existing regulations to explicitly require 510(k) submitters to provide in their 510(k) a summary of all scientific information known or that should be reasonably known to the submitter regarding the safety and/or effectiveness of the device under review."

JIRA's comment is as follows.
The main text of Preliminary Report and Recommendations does not explicitly specify this requirement. In any case, the device under 510(k) review is essentially equivalent to the predicate device. Accordingly, it is redundant to add these requirements. Therefore, delete it.

4) Quality of submission, lack of clarity and training of reviewers

【VOLUME Ⅰ, page 69/119, 5.2.1.2. Quality of submission】

JIRA's comment is as follows.
When reviewers review the software itself or the device that incorporates software, the result often depends on the discretion of reviewers. Sometimes, the guidance and review policy are not consistent.
The guidance should be better compiled and the reviewers should be better trained.
For example, see VOLUME I, Appendix D, Reviewer Survey. Question 6 says in part "Which of the following represent a change in the technological characteristics from the predicate device to the subject device?" About 50% of reviewers surveyed responded that item F represents a change. Item F says " Updating the software in a device to run on Windows 7 instead of Windows XP."
Therefore, reviewers should be trained to have an appropriate level of discretion competence.

October 4, 2010

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

Re: The Center for Devices and Radiological Health's 510(k) Working Group Preliminary Report and Recommendations; Request for Comments (Docket No. FDA-2010-N-0348)

Dear Sir or Madam:

The American Association for Justice (AAJ), formerly known as the Association of Trial Lawyers of America (ATLA), hereby submits comments in response to the Food and Drug Administration's (FDA) Notice regarding the 510(k) Working Group's recommendations to strengthen the 510(k) process. *See* 75 Fed. Reg. 47307.

AAJ, with members in the United States, Canada and abroad, is the world's largest trial bar. It was established in 1946 to safeguard victims' rights, strengthen the civil justice system, promote injury prevention, and foster the disclosure of information critical to public health and safety. AAJ applauds the FDA's efforts to strengthen the 510(k) process. AAJ supports the 510(k) Working Group's recommendations that will make the process safer and more efficient. However, AAJ does not support any recommendation that would lead to preemption of state tort laws. Preemption related to 510(k) devices is contrary to law and a detriment to patient safety.

I. Complex Devices Deserve Increased Scrutiny

A. Preemption of 510(k) Devices is Contrary to Law and Will Decrease Device Safety

AAJ supports any additional controls on the 510(k) process that will increase the safety of medical devices, including the creation of a new sub-category (IIb) with additional requirements and controls and the potential elimination of the use of split predicates. AAJ believes that both of these recommendations have the potential to greatly improve the safety of 510(k) approved devices. Nevertheless, AAJ strongly opposes any additional preemption of state tort laws that may result from these increased controls. Further, the FDA must make clear, in any guidance or regulations issued as a result of this Notice, that state tort claims remain available to patients who are injured by a 510(k) cleared device and are not preempted.[1]

[1] *Medtronic, Inc. v. Lohr*, 51 U.S. 470 (1996).

Medtronic v. Lohr provides the most relevant and persuasive case law on the subject of implied preemption. It supports the proposition that Congress did not seek to preempt common law claims and intend for consumers to have no recourse for defective medical products.[2] The Court found that neither the statutory scheme nor legislative history suggests that the 510(k) process was intended to do anything other than maintain the status quo, which included the possibility that a device's manufacturer would have to defend itself against state law negligent design claims.[3]

In addition, any preemption in regards to medical devices will result in a lack of legal recourse for consumers who have been injured or killed by a defective medical device. If medical device companies are afforded immunity for producing defective devices, injured patients and their families are unable to be made whole after suffering injury and illness. Typically in lawsuits involving defective medical devices, the device manufacturer picks up the cost for medical expenses related to the defective product. However, if these claims are preempted, these costs are shifted to Medicare and the general public pays the costs.[4] Furthermore, when medical device manufacturers are insulated from legal recourse for producing defective devices, there is no longer any incentive to focus on patient safety. As a result, patient safety suffers. Accordingly, the FDA should ensure that Congress's intent is followed by specifically stating that state tort law claims are not preempted should they choose to adopt the new IIb sub-category or eliminate the use of split predicates.

II. The FDA Should Strengthen Its Post-Approval Requirements for the 510(k) Process

A. Purchase/Sale or Transfer in Ownership of a 510(k)

AAJ supports the 510(k) Working Group's recommendation that the FDA develop guidance and regulations regarding appropriately documenting transfers of 510(k) ownership. Currently, the FDA does not keep track of 510(k) transfers in ownership. However, for patient safety, it is imperative that the FDA maintains a record of who currently holds a 510(k). Accordingly, the FDA should follow the 510(k) Working Group's recommendation and develop stronger procedures for monitoring devices that have been through the 510(k) clearance process. The FDA should consider fines and rescission for 510(k) holders who do not comply with reporting requirements.

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[2] *Id.*

[3] *Id.*

[4] *Examining the Sprint Fidelis Effect on Medicare Costs*, H. Dennis Tolley, PhD, ASA (April, 2010).

B. The FDA Should Require Post-Market Surveillance Studies

In addition to keeping apprised of the ownership interests of 510(k)'s, AAJ agrees with the 510(k) Working Group's suggestion that the FDA pursue requiring post-market surveillance studies of medical devices. Although, the FDA currently does not have the explicit authority to require a post-market study as a condition of approval; we agree that the FDA should pursue receiving this authority. Requiring post-market study of certain devices as a part of the 510(k) clearance process is the only way to ensure the safety of many of these devices. In an effort to promote the continuing safety of cleared medical devices and in the interest of patient safety, the FDA should utilize post-market surveillance as vociferously as possible under the law.

C. The FDA Should Pursue the Authority to Rescind a 510(k) Clearance in a Wide Array of Circumstances

AAJ supports the 510(k) Working Group in its recommendation that the FDA pursue issuing a regulation that would define the scope, grounds and procedures for fully and partially rescinding a 510(k) clearance. AAJ believes that the FDA should pursue most expansive allowable rescission authority. There are countless different instances in which it would be appropriate to rescind a 510(k) clearance including: new safety data or information regarding adverse events linked to the device, fraud in the clearance process and problems with the underlying clinical data that was used to clear the device. The FDA has long considered developing regulations that would allow for rescission of a 510(k) clearance under these types of situations.[5] In fact, in 2001 the FDA proposed regulations of this topic that were never finalized.[6] In the interest of patient safety, the FDA should issue regulations that would allow for the rescission of a 510(k) in any circumstance where patient safety is jeopardized.

AAJ appreciates this opportunity to submit comments in response to the 510(k) Working Groups recommendations regarding the 510(k) process. If you have any questions, please contact Sarah Rooney, AAJ's Regulatory Counsel at (202) 944-2805.

Sincerely,

C. Gibson Vance, President
American Association for Justice

[5] 66 F.R. 3523 (2001).

[6] *Id.*

Roche

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

4 October 2010

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,

Roche Diagnostics ("Roche") respectfully submits the following comments on the Center for Devices and Radiological Health ("CDRH") *510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations.* Roche appreciates the tremendous effort that CDRH has undertaken in assessing the strengths and limitations of the 510(k) program, and commends CDRH for focusing on the program's dual aims: (1) To 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) to foster innovation. Roche understands the difficulty in balancing these two aims, and is pleased that CDRH has been able to strike this balance with some of its proposed improvements.

In particular, Roche supports the proposed streamlining of the currently underused *de novo* process. More pre-submission engagement to determine which devices should follow the *de novo* pathway will ultimately foster innovation, as new technologies are more quickly funneled into the appropriate review path.

Roche also applauds CDRH's general focus on science-based education and training of CDRH staff. Such education and training will drive greater consistency and predictability across the 510(k) program. Indeed, if combined with greater education and training of industry, this effort could lead

to a better understanding of expectations, and a more effective partnership between CDRH and industry. Ultimately, it will be the patient who wins with safer, more innovative products.

That said, we share the concern raised by AdvaMed and other industry organizations that the cumulative effect of the more than 70 CDRH proposals contained in the preliminary reports could result in a revolutionary change to the 510(k) program. Roche understands that change and innovation within the medical device industry over the past 30 years necessitates review and modification of the 510(k) program, and that FDA needs to take measures to ensure consistency and predictability throughout the program. Nonetheless, Roche believes that the 510(k) program is well-founded, supports the introduction of safe products, promotes public health, and fosters innovation. The issue is not with the foundation of the program, but with the inconsistency in interpretation of its core elements. For that reason, Roche joins other device manufacturers and industry organizations in encouraging CDRH to solidify the program with better guidance and related training without making a wholesale change to the 510(k) program at this time. With that in mind, we submit the following specific comments for CDRH's consideration.

Intended Use and Indication

Roche agrees with CDRH's focus on clarifying certain terms that fall within the concept of "substantial equivalence." In particular, Roche urges CDRH to maintain the distinction between "intended use" and "indication for use." Although Roche agrees with CDRH that confusion exists regarding what constitutes an "intended use" and "indication," Roche believes the path to resolving this confusion is through clearer definition of each of the terms and consistent application of those definitions. Failure to maintain the separate concepts of intended use and indication will reduce the current flexibility in determining whether a specific indication triggers the need for a PMA or new 510(k) submission.[1] There also is a high likelihood that blending the two concepts will lead to an increase in "not substantially equivalent" ("NSE") determinations. This, in turn, will lead to an increase in the number of unnecessary PMA submissions or *de novo* requests.

Off-Label Use

Roche respectfully disagrees with CDRH's approach to addressing off-label use by requiring that such uses be reviewed as part of a substantial equivalence determination. We believe that such a requirement could chill the environment for new intended uses. Manufacturers may be wary of seeking a new intended use if CDRH also requires the clinical data to support an unintended off-label use.

[1] Food and Drug Administration, *Guidance for Industry: General/Specific Intended Use* (November 4, 1998).

Instead, Roche encourages CDRH to rely on its existing statutory authority to require statements in labeling that limit a device's use for off-label purposes.[2] This provides a more flexible and less onerous alternative for CDRH to follow in protecting public health. In addition, Roche recommends that CDRH use the tools currently available to the agency to curb *promotion* of off-label uses. This will enable CDRH to effectively address its concerns without directly impeding the legally-protected practice of medicine.[3]

Split and Multiple Predicates

Roche has concerns that eliminating the use of "split predicates" and arbitrarily limiting a submission to no more than five predicates could lead to an increase in unnecessary PMA and *de novo* filings, and negatively impact the introduction of innovative new devices that promote the public health. Although the use of split or multiple predicates may not be appropriate in all cases, in many instances it provides a reasonable and practical approach to establishing substantial equivalence. For example, combining the functionality of two existing devices or a device and its accessory into a single device would mean reliance upon split or multiple predicates, which, in most cases, would be reasonable. Consider as an example:

- A point-of-care diagnostic device works with a physically-separate accessory device reader that downloads stored data to generate standardized reports. A manufacturer designs a new device that incorporates the diagnostic device and embeds portions of the device reader into the same housing and firmware. This very well could require reliance on split or multiple predicates in establishing substantial equivalence. A restriction on split or multiple predicates may mean this innovative new device would be subject to a *de novo* or PMA submission, rather than 510(k) review.

Rather than prohibiting the use of split predicates and limiting the use of multiple predicates, Roche asks CDRH to consider establishing a risk-based guidance that provides criteria defining when the use of split or multiple predicates might be appropriate. Such guidance could require 510(k) sponsors to justify the need for split or multiple predicates, enabling CDRH to determine on a case-by-case basis whether the use of such predicates makes sense. This approach would provide

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[2] 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 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." 21 U.S.C. § 360c(i)(1)(e)(i).

[3] *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001).

the agency and industry greater flexibility to address innovative new technologies.

In addition, Roche proposes that CDRH consider using the five-predicate limit as a recommended maximum, but retain the flexibility to allow 510(k) sponsors to propose and justify additional predicates. Roche is concerned that prohibiting more than five predicate devices as a matter of course could lead to unnecessary PMA's and *de novo* requests, particularly for complex multiplex devices, microarrays, sequencers and other new, yet-to-be-seen technologies. Providing guidance that allows 510(k) sponsors to propose and justify additional predicates, on the other hand, would provide CDRH the flexibility to consider whether a review of additional predicates raises unnecessary risks, without stifling innovation.

Class IIb Subset

Roche understands the need for guidance to bring transparency, predictability and consistency to the 510(k) process. That said, Roche joins many others within industry who are concerned about the establishment of a new "class IIb." Roche urges CDRH to focus on providing guidance for specific higher-risk device types rather than establishing a new device class. Roche further recommends that CDRH consider designating such a guidance document as a Special Control after the agency has an opportunity to gain practical experience in using the guidance document.

This approach would be consistent with CDRH's prior treatment of specific devices that raise higher risks. CDRH, for example, has issued such guidance documents as: "Review Criteria Assessment of Portable Blood Glucose Monitoring In Vitro Diagnostic Devices Using Glucose Oxidase, Dehydrogenase or Hexokinase Methodology," "Guidance for Industry and FDA Staff: Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions," and "Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Cardiac Allograft Gene Expression Profiling Test Systems." Roche strongly encourages CDRH to take this path to defining expectations for narrowly-defined, specific groups of higher-risk devices that fit within the 510(k) program but raise a higher level of risk. In addition, as CDRH develops its guidance, Roche believes the focus should be on what evidence CDRH feels it needs to establish substantial equivalence, and what special controls may be appropriate to mitigate the risk. This will enable the agency to support both of its aims: To protect public health, while fostering innovation.

As CDRH clarifies its evidentiary and submission requirements for these specific higher-risk devices, and becomes more comfortable with the industry's ability to mitigate the associated risk, Roche also encourages CDRH to consider down-classifying some devices that currently are subject to PMA due to the risk associated with the devices. Provided CDRH took a risk-based approach within the 510(k) program, which the agency appears to be doing, many higher-risk devices could

fit within the 510(k) program, or the *de novo* process. For example, continuous interstitial glucose monitoring devices feasibly could fit within this subset of devices.

As CDRH looks beyond its short-term proposals to the long-term future of the 510(k) program and risk-based device classification, we recommend that CDRH consider harmonization with the principles of the Global Harmonization Task Force ("GHTF"), including adoption of the GHTF classification of devices.

Rescission

Roche understands the need for FDA oversight of the medical device market and supports consistent and equitable application of FDA enforcement authority. However, Roche joins AdvaMed and many other device manufacturers in expressing concern with increasing CDRH authority to rescind a 510(k) clearance. Our concerns are two-fold:

- CDRH rescission of a 510(k) would imply that the underlying design and associated intended use are fundamentally flawed, meaning either that the data submitted in the 510(k) or FDA's assessment of the data was incomplete, incorrect, or flawed. CDRH already has adequate authority to enforce existing regulations and laws associated with incomplete or incorrect information under 21 CFR 807.87(k). Further, CDRH already has substantial authority to monitor and enforce existing laws and regulations related to adulterated or misbranded devices and can up-classify a device as needed based on new safety information.[4]

- The act of rescinding a 510(k) could have significant unintended consequences upon the market and upon the agency. For example, significant thought and guidance would be needed to understand:
    - How a rescinded 510(k) would impact both devices directly related to the 510(k) and other devices using the rescinded device as a predicate device. Would the agency require active withdrawal of such devices from the market?
    - How would a manufacturer be notified? Would the manufacturer have the opportunity to contest the decision or present additional information to FDA prior to a final decision? Would the notification be publicly disclosed?
    - What guidance would FDA offer to manufacturers discovering that their predicate device 510(k) was rescinded for a soon-to-be filed or pending 510(k)? How would CDRH reviewers be required to react to a pending 510(k) under the same situation?

[4] 21 U.S.C. § 360c.

Roche

General Comments

Roche recognizes that CDRH cannot maintain the status quo. We also realize that CDRH needs the flexibility to shift its regulatory interpretations as innovative technology presents new challenges. However, Roche is troubled by shifts in interpretation that place higher standards and more restrictive requirements on new, often better, technologies, while older but similar technologies remain in the market unaffected. This delays innovative new products that might be safer and more effective, and could encourage off-label use of existing technologies. As CDRH moves forward with 510(k) reform, we encourage the agency to address this incongruence.

In addition, we urge CDRH to provide adequate time for both the agency and industry to transition to new interpretations and expectations. At the macro level, CDRH's proposals, if fully implemented, will require enormous resources, education and training of both the agency and industry. At the micro level, each change in interpretation will require a transition period to enable the agency and industry to adjust to the changing expectations. This transition period will be critical to ensuring smooth implementation of CDRH's modifications.

Finally, Roche is committed to working with CDRH throughout the change process. We offer our assistance and support, particularly with respect to the distinct issues impacting *in vitro* diagnostics.

Respectfully yours,

Roche Diagnostics

Danelle R. Miller
Legal Counsel Global Quality
and Regulatory Affairs

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Lilly Corporate Center
Indianapolis, IN 46285
U.S.A.

Phone 317 276 2000

October 04, 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,
CDRH 510(k) Working Group Preliminary Report and Recommendations

Eli Lilly and Company is pleased to comment on the CDRH 510(k) Working Group Preliminary Report and Recommendations. Major changes are being proposed, and we are grateful for the opportunity to provide input.

A number of the proposals would be beneficial to public health, particularly recommendations for enhancing FDA reviewer training, providing clarity to key terms, streamlining the de novo process, and improving guidances. Many of the recommendations are very general in nature and their impact will be very difficult to evaluate until specifics are provided. For this reason, we urge the agency to provide those written details and allow comments from stakeholders in all instances, following established Good Guidance Practices for those proposals brought forward by way of guidance. We believe it would be a serious mistake to take final actions based upon stakeholder comments on proposals which are conceptual and quite naturally vague at this stage. In this regard, there are instances where we may support the general concepts contained in the report but reserve the right to oppose or object future specific proposals which provide detail to those general comments.

The reports acknowledge that many changes will require rulemaking or legislation. It is important to recognize that simultaneous implementation of multiple changes would disrupt a process that is an essential step in the availability of new medical technologies. Any changes that FDA pursues should be implemented so as to minimize disruption of the current 510(k) process. It is possible that the forthcoming Institute of Medicine (IOM) report will also recommend changes in regulation or law. We recommend that action on proposals which do not have clear current stakeholder consensus be deferred until the IOM report and any necessary congressional activity can also be considered. Such an approach would avoid the unnecessary burden that would be placed on industry and the health care system from multiple, separate activities.

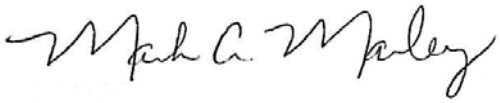
The report clearly establishes that FDA s current training of its staff is ineffective in many respects, and that many of its guidance documents are not sufficiently clear. Unless these root causes of shortcomings in the 510(k) process are addressed, no change to the program can achieve meaningful improvement.

Finally, we stress the importance of working toward regulatory convergence globally, so that regulatory approvals are achieved via substantially similar processes and standards. To this end and to the extent permitted by law, we recommend that CDRH consider harmonization with the principles of the Global Harmonization Task Force, including adoption of the GHTF definition of clinical data[1] (which is consistent with FDA's definition of "valid scientific evidence") and consideration of, other regulatory approvals" particularly those that result from sophisticated review processes.

The attached comments are focused on the proposed recommendations of highest concern to us, either because we disagree with the proposal, or because we feel more details are needed before we can provide constructive input.

Please contact me at (317) 277-0192 for clarification of any comments

Sincerely,



Mark A. Marley
Eli Lilly and Company
Regulatory Affairs

[1]GHTF Study Group 5 Final Document Study Group 5 Final Document SG5/N1R8:
"Clinical Data Definition: Safety and/or performance information that are generated from the clinical use of a medical device.
Explanation: Sources of clinical data may include:
(i) Results of pre- and postmarket clinical investigation(s) of the device concerned
(ii) Results of pre- and postmarket clinical investigation(s) or other studies reported in the scientific literature of a justifiably comparable device
(iii) published and/or unpublished reports on other clinical experience of either the device in question or a justifiably comparable device"

Formation of Class IIb:

"CDRH should take steps through guidance and regulation to facilitate the efficient submission 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." [CDRH 510(k) Working Group Preliminary Report and Recommendations, Volume I, Recommendation 5.2.1]

"…the Working Group recommends that CDRH explore the possibility of developing 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 to support a substantial equivalence determination. Delineating between "class IIa" and "class IIb" would not reconfigure the current, three-tiered device classification system established by statute; it would represent only an administrative distinction. The development of a "class IIb" guidance would provide greater clarity regarding what submitters would generally be expected to provide in their 510(k)s for certain types of devices. Although further deliberation would be needed to better characterize "class IIb," potential candidates for this device subset may include implantable devices, life-sustaining devices, and life-supporting devices, which present greater risks than other class II device types." [CDRH Volume I, Section 1.1, p. 5]

Lilly Comments:

We agree that Class II devices have a range of risk profiles. Some Class II devices already require additional special controls. We do not agree that the formation of "class IIb" would provide greater clarity regarding what submitters would be expected to provide in their 510(k)'s. We support FDA's efforts to enhance predictability by providing guidance on which devices require additional special controls. We believe FDA's efforts should be focused on proposing additional special controls for a narrow list of specific higher risk device types where there is adequate justification, instead of creating the proposed "class IIb". In addition, as CDRH develops these guidance documents, we believe the focus should be on what evidence CDRH feels it needs to establish substantial equivalence, and what special controls may be appropriate to mitigate the risk.

We are concerned that there is a high probability that a broadly defined "class IIb" would result in less predictability in the application of appropriate regulatory requirements for the determination of substantial equivalence, especially in light of FDA's comments that "the delineation between "class IIa" and "class IIb" is meant to be a general guideline only." Therefore, we urge CDRH to avoid a "class IIa/IIb" distinction and focus on providing special controls in regulatory guidance for each of the higher risk specific device types to be identified by FDA.

In general, we believe that clinical trials should only be required for Class II devices if safety and effectiveness cannot be confirmed by non-clinical methods (e.g. bench testing, human factors studies) and there isn't adequate clinical information available internally or in the public domain for a similar device and intended use. We support the appropriate use of postmarket studies for specified higher risk devices, but we do not support the recommendation to "potentially seek greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices" [CDRH Volume I, Section 1.1, p. 12] In light of the existing authority to include postmarket studies in premarket special controls and through Section 522, further authority is unnecessary. It also seems that FDA would need formal regulatory or statutory authority to make such a change.

We do not agree that additional manufacturing information should be necessary to support substantial equivalence determination for Class II devices. For our Class II devices, we feel the existing 510(k) guidance and consensus standards provide an adequate framework for providing the information needed to support SE determination. We encourage FDA to develop appropriate guidance on a case-by-case basis, describing manufacturing information it believes is necessary to establish substantial equivalence for specific higher risk device types.

Substantial Equivalence

"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." [CDRH Volume I, Section 1.1, p.7]

"The 510(k) Working Group recommends that CDRH reconcile the language in its 510(k) flowchart … with the language provided in section 513(i) of the Federal Food, Drug, and Cosmetic Act (21 USC §360c(i)) regarding "different technological characteristics" and "different questions of safety and effectiveness."

"…explore the possibility of pursuing a statutory amendment … 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." [CDRH Volume I, Section 1.1, p.8]

"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." [CDRH Volume I, Section 1.1, p. 9]

Lilly Comments:

We believe it is beneficial to maintain distinct terms for "indication for use" and "intended use". Indications for use are subsets within intended use. These two terms are distinct and enable increased clarity regarding the device use. Although we agree with CDRH that confusion exists regarding what constitutes an "intended use" and "indication for use," we believe the path to resolving this confusion is through clearer definition of each of the terms within current concepts and more consistent use of these terms by the agency and all stakeholders. With that in mind, we recommend defining the two separate terms, by regulation if needed, to ensure clarity but not to change the underlying definitions. Failure to maintain the separate concepts of intended use and indication will reduce, if not eliminate, the current flexibility in determining whether a specific indication triggers the need for a PMA or new submission. There also is a high likelihood that blending the two concepts will lead to an increase in unnecessary "not substantially equivalent" ("NSE") determinations. This, in turn, will lead to an increase in the number of unnecessary PMAs or *de novo* classification requests.

With regard to revising the 510(k) flowchart, we encourage FDA to propose guidance to clarify the various decision points in the flowchart. If FDA proposes changes to the decision process, then notice and comment procedures would be required before implementing any changes.

We do not agree that a statutory amendment is needed regarding additional FDA authority for oversight of off label use. We have no objection to FDA developing guidance to provide greater clarity for reviewers to identify when there is a reasonable likelihood that the device will be used for an intended use other than that in the proposed labeling and when that use could cause harm, however, 510(k) review and clearance should not be negatively impacted by potential off-label use issues. Any such change should not change the current regulatory or statutory schema. As is the case with current FDA practice, a precaution statement can indicate that an off label use has not been studied in the clearance for the device.

A properly administered 510(k) program ensures that devices receiving FDA clearance are suitable to the intended use in the proposed labeling and for which they are being cleared. Likewise, in the postmarket period, the agency has the ability to deal with manufacturers that engage in off-label promotional activities. Specifically, 21 CFR 801.4 provides the agency with considerable discretion in identifying off label uses and company activities geared toward promoting them. When such situations arise, FDA can take many actions to ensure compliance with applicable requirements.

Disallowing the use of "split 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. For this reason and those described below, we respectfully disagree with these CDRH recommendations.

Although the use of split predicates may not be appropriate in all cases, in many instances it provides a reasonable and practical approach to establishing substantial equivalence. Rather than eliminating the use of split predicates, we believe CDRH should define when and under what circumstances use of split predicates might be appropriate. CDRH could establish guidance based on risk, and require 510(k) sponsors to justify the need for split predicates. This approach would provide both the agency and industry greater flexibility to deal with innovation as it occurs.

Unreported Device Modifications

"The 510(k) Working Group recommends that CDR H 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)." [CDRH Volume I, Section 5.2.1.1]

"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." [CDRH Volume I, Section 1.1]

Lilly Comments:

We believe that the current FDA Guidance, "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)" is an adequate framework for deciding when a new 510(k) is needed. This guidance is almost 15 years old, but it has remained relevant throughout the evolution of device technology.

The above referenced guidance clearly obligates manufacturers to notify the Agency of significant changes through the submission of a new 510(k), and we believe that requiring manufacturers to report "any modifications made to its device without the submission of a new 510(k)" is an unnecessary burden for both the Agency and industry. We already maintain records of changes per QSR requirements, which are subject to FDA inspection.

If the agency feels there is a genuine public health need on a subset of higher risk 510(k) products, the agency could consider, subject to further comment and input, requiring the periodic reporting of defined modifications for products in the subset. Those reports should exclude *de minimus* changes so that truly minor or trivial changes do not need to be reported.

Quality of Submissions

"The 510(k) Working Group recommends that CDRH consider adopting the use of an "assurance case" framework for 510(k) submissions." [CDRH Volume I, Section1.1, p. 10]

"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." [CDRH Volume I, Section1.1, p. 10]

"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." [CDRH Volume I, Section1.1, p.11]

"The 510(k) Working Group recommends that CDRH 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." [CDRH Volume I, Section1.1, p.13-14]

Lilly Comments:

We believe the assurance case framework may be a useful tool and may make sense in some cases, but because many other established and suitable processes are available it should be only an optional tool if implemented at all. It may not always add value to the review, and would increase the required resources for both industry and the agency without improving public health.

We agree with FDA that photographs can enhance understanding of a product, its function, and its relation to predicate devices. We believe that pictures or diagrams combined with well written descriptions are the best way to provide an overview of our devices and to convey the way they are used. We believe that schematics should only be included if pictures and verbiage are not adequate to provide supporting rationale for the substantial equivalence determination. Schematics would likely be considered proprietary information; thus, would not be appropriate for the proposed enhanced public 510(k) database.

We agree with FDA's desire to have sufficient scientific information on a product to make well-informed decisions. However, the proposal by FDA to require 510(k) submitters to provide a list and description of all scientific evidence regarding safety and effectiveness of a device that is known to or that should be reasonably known to the submitter is unreasonably burdensome to both FDA and industry. It should be noted that the 510(k) submitters are already required to submit all relevant information (see for example 21 USC 360c(i)) and to certify that "[T]he submitter believes, to the best of his or her knowledge" that no material fact has been omitted" (21 CFR 807.87(k)). Even without the inclusion of unpublished clinical data or pre-clinical testing, this represents an almost impossibly large volume of data to list, describe and effectively summarize, especially when much of the data may be irrelevant or redundant with regards to the particular device or to substantial equivalence. In addition, the FDC Act specifically limits the information that FDA can request to "information that is necessary to make a substantial equivalence determination," so the proposed additional data is outside the current statutory framework. For scientific/clinical information that is necessary for the determination of substantial equivalence, we recommend a summary of clinical evidence that is consistent with the GHTF Study Group 5 document on Clinical Evaluation and the recent MEDDEV 2.7.1, both of which narrow the scope of the relevant device specific information to a summary of *relevant* literature and *pertinent* clinical data, rather than an exhaustive list of all information.

Regarding the proposal to require electronic submission of final device labeling and subsequent periodic updates, we request clarification from FDA. Is FDA planning to request submission of the final label wording and graphics, or the final printed labeling? Logistically it would be more difficult for us to provide the final printed labeling, so we are seeking further clarification.

Unique Device Identification

"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."[CDRH Volume I, Section5.2.1.3, p.79]

Lilly Comments:

In general we support UDI, which could have potential benefits such as improved surveillance and execution of recalls. It's not clear in the 510(k) Working Group's recommendations how UDI could be linked to health outcomes, or how this could be incorporated into the premarket submission process. We request FDA provide more information on their potential objectives and uses of the pooled outcomes data.

novo nordisk®

General Correspondence
CDRH 510(k) Working Group Preliminary Report and Recommendations

September 29, 2010

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

RE: Docket No. 2010-N-0348

CDRH 510(k) Working Group Preliminary Report and Recommendations

Dear Sir/Madam:

Novo Nordisk Inc. appreciates the opportunity to provide comments to the above-referenced docket on the CDRH 510(k) Working Group Preliminary Report and Recommendations.

Novo Nordisk is a pioneer in biotechnology and a world leader in diabetes care and has a leading position within areas such as hemostasis management, growth hormone therapy, and hormone therapy for women. Novo Nordisk manufactures and markets pharmaceutical products, medical devices, and services that make a significant difference to our patients, the medical profession, and society.

After reviewing the CDRH 510(k) Working Group Preliminary Report and Recommendations, we identified several areas which warrant comment, as detailed below.

Intended use to support substantial equivalence

In Section 5.1.1.1., "Same Intended Use," the report discusses a sponsor's device having the same intended use as a predicate device to support a substantial equivalence determination. The report also notes confusion with the terms "intended use" versus "indications for use," and recommends that CDRH revise existing guidance to consolidate the two terms into a single "intended use" term. The report further states that the intended use of a device is based on the device's proposed labeling but notes cases where CDRH may determine that there is a "reasonable likelihood" that a device may be used for uses other than those detailed in the proposed labeling.

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We agree that CDRH should provide additional guidance regarding the term "intended use" to address confusion between that term and "indications for use," and recommend that the Center clarify the components of substantial equivalence. Regarding potential off-label use of devices referenced in the report, we recommend that CDRH provide guidance on how it determines that there is a "reasonable likelihood" that a device is intended to be used off-label.

Concerns about predicate quality

In Section 5.1.2.1, "Concerns about predicate quality" and in other areas of the report, the predicate selection process is noted as a root cause for low quality submissions. The report recommends that CDRH provide guidance on when a device should no longer be used as a predicate because of safety or efficacy concerns.

We agree with the report's recommendation to provide guidance on when a device should not be used as a predicate, and recommend that the guidance include detailed instructions on reviewing the safety profile of potential predicate devices. Additionally, we recommend that the guidance clarify that it is still acceptable to use an earlier, discontinued model of a cleared device as a predicate.

Split predicates and multiple predicates

In Section 5.1.2.3, "Use of Split Predicates and Multiple Predicates," the report states that using "multiple predicates" is when a sponsor compares its device to more than one predicate to show that each functional component of the device is substantially equivalent to its corresponding predicate. The report also covers the use of "split predicates," where a sponsor attempts to show that its device has the same intended use as one predicate and the technological characteristics of another. The report notes that CDRH has accepted the use of multiple predicates and recommends that the Center provide guidance on when multiple predicates may be used. Further, the report recommends that CDRH consider prohibiting the use of split predicates.

We agree with the recommendation to provide guidance for using multiple predicates, and recommend that such guidance provide a detailed overview for the use of multiple predicates with the same intended use as the sponsor's device. We also support the recommendation for disallowing the use of split predicates, as these predicates may not provide adequate safety and efficacy information about a sponsor's device.

Quality of submissions

In Section 5.2.1.2, "Quality of Submissions," the report recommends that CDRH implement an Assurance Case Framework for 510(k) submissions, to provide a formal method of showing the

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validity of claims. The report further recommends that the Center provide guidance on this topic to help industry use assurance cases to support predicate comparisons.

We realize that FDA intends to use assurance cases to address possible device hazards, and we recommend that CDRH guidance on assurance cases exempt minor changes to 510(k) cleared devices that have been safely on the market. We see a potential burden for both industry and FDA if assurance cases were mandated for all 510(k) cleared devices when many of these devices have already demonstrated their safety in the marketplace. Additionally, we feel that CDRH should limit the assurance case framework to Class IIb devices, rather than requiring the framework for all Class II devices.

Secondly, Section 5.2.1.2 also discusses the proper use of FDA-recognized consensus standards. We would like to call attention to the fact that multiple international standards are not currently recognized by FDA and that the report does not refer to Global Harmonization Task Force (GHTF) guidance in its recommendations. We recommend that FDA be more proactive in recognizing international standards, GHTF guidance, and information from other national health authorities to help strengthen the 510(k) process. We also advise that CDRH be more active in updating its database with recognized global standards. Finally, we recommend that CDRH clarify that 510(k) files currently under FDA review should not be impacted by the issuance of new standards or the Agency's new endorsement of global standards.

Product codes

In section 5.2.2.1, "Product Codes," the report evaluates its three-character system for product codes and recommends that CDRH develop Standard Operating Procedures and conduct training to standardize the development of product codes.

We support the proposals for improving processes related to product codes, however, we would also recommend that CDRH incorporate the use of Global Medical Device Nomenclature (GMDN) codes and ISO 15225, "Nomenclature, Specification for a nomenclature system for medical devices for the purpose of regulatory data exchange." As most companies market products internationally, we feel that the Center and industry would benefit from a global harmonization of product codes.

Class IIb device subset

In Section 5.2.1.3, "Type and Level of Evidence Needed," the report recommends providing guidance to develop a Class IIb subset of devices, which would normally require clinical information, manufacturing information, or possibly postmarketing evaluations to support a substantial equivalence determination.

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We have concerns with Class IIb devices potentially requiring postmarketing evaluations to manage risks. Since a cleared Class II device would be determined to be substantially equivalent to a predicate device, future postmarket data to address potential risks should not be required.

Third-party review

In section 5.3.1.2, "Third-Party Review," the 510(k) process third-party review program is analysed. The report recommends that CDRH enhance this program through training initiatives and examining options for sharing additional information with third party reviewers.

We support the report's recommendations for improving the third-party review program, as the program is beneficial for an effective device clearance program. We expect that third-party reviews would be beneficial for manufacturers outside of the US, such as companies in the European Union that might use their Notified Bodies (the number of FDA-qualified reviewers in these organizations has been a limiting factor). Sharing additional information with third-party reviewers, such as product knowledge and company insights, would contribute to a more effective third-party review program.

Novo Nordisk fully supports FDA's efforts to assess and strengthen the 510(k) process. We appreciate your consideration of our comments on the CDRH 510(k) Working Group Preliminary Report and Recommendations.

Sincerely,

Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
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October 4, 2010

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

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 Indiana Medical Device Manufacturers Council represents more than 60 manufacturers of medical devices in the state of Indiana. Our members employ more than 15,000 people, making our state the 8th largest in terms of medical device employment. We have the fifth highest concentration of medical technology employment as measured by our industry's share of total state employment. Consequently, major changes in government policies that affect the ability of our members to develop and market new products are very important to us. We are grateful to have the opportunity to comment on the reports of the FDA's 510(k) Working Group and Task Force on the Utilization of Science in Regulatory Decision Making.

IMDMC commends the 510(k) Working Group and Task Force for their efforts. Since its inception over 30 years ago, the 510(k) process has worked well for all affected stakeholders -- providing FDA with incredible flexibility in effectively regulating the medical device industry as it develops and markets products that allow health care practitioners to safely and effectively care for patients, thereby improving the public health. Despite this lengthy record of success, FDA has proposed more than seventy Working Group recommendations which could have a very significant impact on the ability of manufacturers to bring new devices to patients. We will share our views and concerns about several of those proposals below.

In General
The report makes it clear that the FDA has taken a thoughtful look at many facets of the 510(k) program. A number of proposals would be beneficial to public health, particularly recommendations for enhancing reviewer training, providing clarity to key terms, streamlining the de novo process, and improving guidance documents.

The report also includes discussion of the manner in which proposed changes could be implemented. The report acknowledges that many changes will require rulemaking or legislation. However, we do not believe the correct conclusions have been reached in all cases. In several instances, the report

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suggests that changes might be made without the rulemaking activity that to us seems necessary. In other cases, it is not clear that FDA currently has legal authority for changes that are proposed, without new legislation. IMDMC does not believe that FDA should pursue activities at this time that would require new legislation.

Additionally, many of the recommendations are very general in nature and their impact will be very difficult to evaluate until specifics are provided. For this reason, we urge the agency to provide those written details and allow comments from stakeholders in all instances, following established Good Guidance Practices for those proposals brought forward by way of guidance. We believe it would be a serious mistake to take final actions based upon stakeholder comments on proposals that are conceptual and quite naturally vague at this stage. In this regard, there are instances where IMDMC may support the general concepts contained in the report but reserves the right to oppose or object to future specific proposals that provide the important detail necessary to fully understand the impact of the more general recommendations.

Also, it is important to recognize that simultaneous implementation of multiple changes would disrupt a process that is an essential step in the availability of new medical technologies. Any changes that FDA pursues should be implemented so as to minimize disruption of the current 510(k) process. It is possible that the forthcoming Institute of Medicine (IOM) report also will recommend changes in regulation or law. We recommend that action on proposals that do not have clear current stakeholder consensus be deferred until the IOM report is published and any necessary congressional activity can also be considered. Such an approach would avoid the unnecessary burden that would be placed on industry and the health care system from multiple, separate activities.

The report clearly establishes that FDA's current training of its staff is ineffective in many respects, and that many of its guidance documents are not sufficiently clear. Unless these root causes of shortcomings in the 510(k) program are addressed, no change to the program can achieve meaningful improvement.

Finally, IMDMC wishes to stress the importance of working toward regulatory convergence globally, so that regulatory approvals are achieved via substantially similar processes and standards. To this end and to the extent permitted by law, we recommend that CDRH consider harmonization with the principles of the Global Harmonization Task Force, including adoption of the GHTF definition of clinical data (which is consistent with FDA's definition of "valid scientific evidence) and consideration of other regulatory approvals – particularly those that result from sophisticated regulatory review processes.

De Novo Classification

Proposal: The Working Group recommends that CDRH revise existing guidance to streamline implementation of de novo classification and clarify evidentiary expectations. Further, the task force recommends that CDRH consider exploring the possibility o f generic controls that could serve as baseline specific controls for devices classified in Class II through the de novo process.

Comment: IMDMC believes that the *de novo* classification process is very important and has been underused. We fully support the Working Group's recommendations to streamline and clarify the process. Current guidance calls for a complete 510(k) review even in cases in which it is clear that

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there is no predicate, and we believe this should be changed. The suggestion to instead truncate any 510(k) review as soon as it is clear there is no predicate and to provide guidance on issues to be addressed in a *de novo* submission makes good sense. It may be even better to bypass any 510(k) submission in those cases in which it is clear that there is no predicate device. Current guidance also calls for a second 510(k) to resolve any remaining issues of safety and effectiveness before a *de novo* submission. This is an unreasonably long pathway, and should be replaced with a shorter process. We recommend that FDA immediately proceed to a substantive de novo review for any 510(k) review in which the firm has conceded that there is no adequate predicate. Similarly, the requirement to create new regulations for any device classified by de novo should be reconsidered, to the extent possible.

The recommendation of developing possible generic baseline special controls for *de novo* Class II devices seems unlikely to be practical, given the variety of device types in existence. We also note that the courts have been reluctant to permit application of generic approaches to device-specific issues. With that in mind, we recommend that special controls under *de novo* be specific to each newly classified device type.

As with many FDA processes, training of review staff and industry in the *de novo* process is essential.

Off-Label Use

Proposal: The working Group suggests exploring the possibility of a statutory change to provide the agency with authority to consider off-label use when determining intended use.

Comment: The law allows licensed health care providers to practice medicine, including prescribing and using devices off-label.[1] Furthermore, it is recognized that off-label use by physicians often provides an important benefit in patient care.[2] With the enactment of FDAMA, Congress has specified the approach the agency is to take when concerns arise regarding potential off label use of devices undergoing 510(k) review. We believe that a new requirement would chill the environment for new intended uses. Indeed, manufacturers may be wary of seeking a new intended use if CDRH could require the clinical data to support an unintended off-label use. We simply do not see within CDRH's proposals or elsewhere the evidence that such a change in the program is justified.

While we have no objection to FDA developing guidance to provide greater clarity for reviewers to identify when there is a reasonable likelihood that the device will be used for an intended use other than that in the proposed labeling and when that use could cause harm, 510(k) review and clearance should not be negatively impacted by potential off-label use issues. Any such guidance should not change the current regulatory or statutory schema. As is the case with current FDA practice, a precaution statement can indicate that an off label use has not been studied or considered in the clearance for the device.

A properly administered 510(k) program ensures that devices receiving FDA clearance are suitable to the intended use in the proposed labeling and for which they are being cleared. Likewise, in the

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[1] "[T]he FDCA expressly disclaims any intent to directly regulate the practice of medicine, see 21 U.S.C. § 396 (1994 ed., Supp. IV); and "[ ] off-label use is generally accepted." BUCKMAN CO. V. PLAINTIFFS' LEGAL COMM. (98-1768) 531 U.S. 341 (2001).

[2] "FDA itself recogniz[e] the value and propriety of off-label use" Beck & Azari, FDA, *Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 Food & Drug L. J. 71, 76–77 (1998).

postmarket period, the agency has the ability to deal with manufacturers that engage in off-label promotional activities. Specifically, 21 CFR 801.4 provides the agency with considerable discretion in identifying off label uses and company activities geared toward promoting them. When such situations arise, FDA can take many actions to ensure compliance with applicable requirements.

Many companies are troubled by the inability to make progress in gathering data adequate to support a change in labeling relating to off-label use. IMDMC encourages FDA to adopt procedures that streamline companies abilities to conduct clinical trials in the U.S. and to look for alternatives to prospective, controlled clinical trials for FDA authorization and approval of off-label uses.

Condition of Approval Studies

Proposal: The Working Group recommends that CDRH explore greater use of postmarket authorities that could potentially include seeking greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices.

Comment: Although IMDMC supports the appropriate use of postmarket studies for specified higher risk devices, we do not support the 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 include postmarket studies in premarket special controls and through section 522, further authority is unnecessary. It also seems that FDA would need formal regulatory or statutory authority to make any such change.

Definition of Substantial Equivalence

Proposal: The Working Group recommends that CDRH clarify the meaning of "substantial equivalence" and improve guidance and training for reviewers, managers and industry. The Working Group also seeks clarification of the terms "same intended use" and "different questions of safety and effectiveness." The report further proposes the consolidation of the concepts of "indication for use" and "intended use" into a single term—"intended use."

The 510(k) Working Group also recommends that CDRH reconcile the language in the 510(k) flowchart with language in FD&C Act § 513(i) regarding "different technological characteristics" and "different questions of safety and effectiveness."[3] Further, the report recommends that CDRH revise existing guidance to provide clear criteria for identifying "different questions for safety and effectiveness" and to identify a core list of technological changes that generally raise such questions.

Comment: IMDMC believes the agency should not make any changes to the concepts of intended use and indication for use, and certainly should not combine the terms. The terms have important different meanings. Instead, IMDMC urges CDRH to continue using these terms that have been applied in the 510(k) review process for more than twenty-five years. Although IMDMC agrees with CDRH that confusion exists regarding what constitutes an intended use and indication for use, IMDMC believes the path to resolving this confusion is through clearer definition of each of the terms within current concepts and more consistent use of these terms by the agency and all stakeholders. With that in mind, IMDMC recommends defining the two separate terms, by regulation if needed, to ensure clarity but not to change the underlying definitions. Failure to maintain the separate concepts of

[3] FD C Act and regulations refer to different technological characteristics and different questions of safety and effectiveness, while the 510(k) flowchart refers to new characteristics and new types of safety or effectiveness questions.

intended use and indication for use will reduce, if not eliminate, the current flexibility in determining whether a specific indication triggers the need for a PMA or new submission. There also is a high likelihood that blending the two concepts will lead to an increase in unnecessary "not substantially equivalent" ("NSE") determinations. This, in turn, will lead to an increase in the number of unnecessary PMAs or *de novo* classification requests.

IMDMC doubts that the agency would be able to legally consolidate the terms without providing public notice and an opportunity to comment. Specifically, case law supports the premise that if a new agency policy represents a significant departure from long established and consistent practice that substantially affects the regulated industry, the agency essentially has engaged in rulemaking and is obligated to submit the change for notice and comment. Although the statute and the regulations refer to the term "intended use," the agency's 510(k) program has, since 1976, focused on indications for use as subsets within intended uses. In particular, "intended use" became an umbrella concept that could cover a number of "indications for use" and as a result, a new device may be substantially equivalent to a predicate even though it does not have identical indications for use. Insofar as the consolidation of the terms would change the practice of allowing devices to have different indications for use than their predicates, we believe the agency would be required to submit the change for notice and comment.

With regard to the 510(k) flowchart, IMDMC encourages FDA to issue guidance to clarify the various decision points in the flowchart. However, if FDA proposes changes to the decision process that are new or substantive, then notice and comment procedures would be required prior to implementing any changes. IMDMC offers to work with CDRH in developing any revisions to this important guidance document.

Assurance Case

Proposal: The working group recommends that CDRH consider adopting the use of an "assurance case" framework for 510 (k) submissions.

Comment: IMDMC believes the assurance case approach could be a useful tool and may make sense in some cases, but because many other established and suitable processes are available, it should be only an optional tool if implemented at all. It may not always add value to the review, and would increase the required resources for both industry and the agency without improving public health. In any instance, there should be training and the implementation should be piloted on a small group with appropriate lead times for broader implementation.

Periodic Reporting Requirements – All 510(k) Device Modifications

Proposal: The 510(k) Working Group 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 below, for example, and expanding it to a larger set of devices over time.

Comment: IMDMC opposes periodic reporting to CDRH of all modifications that do not trigger a 510(k) submission. The agency already has access to such information through a number of mechanisms, including subsequent submissions and inspections.

If the agency feels there is a genuine public health need on a subset of higher risk 510(k) products, the agency could consider, subject to further comment and input, requiring the periodic reporting of a subset of modifications for products in that new subset.
In any situation where the agency may decide to require periodic reports of modifications not requiring 510(k) clearance, the agency must establish a de minimis category of changes so that minor or trivial changes do not need to be reported. Otherwise the agency and industry will be overwhelmed with irrelevant, insignificant information that does nothing to protect the public health.

Formation of Class IIb

Proposal: The working Group recommends that CDRH explore the possibility of developing 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 to support a substantial equivalence determination. Delineating between "class IIa" and "class IIb" would not reconfigure the current, three-tiered device classification system established by statute; it would represent only an administrative distinction. The development of a "class IIb" guidance would provide greater clarity regarding what submitters would generally be expected to provide in their 510(k)s for certain types of devices. Although further deliberation would be needed to better characterize "class IIb," potential candidates for this device subset may include implantable devices, life-sustaining devices, and life-supporting devices, which present greater risks than other class II device types.

Comment: Recognizing that the Class II category includes devices with many different risk profiles, we concur with FDA that certain higher risk Class II devices may require more stringent special controls than others. IMDMC understands the need for guidance to bring transparency, predictability and consistency to the 510(k) process. Without a doubt, many of our members have experienced stops and starts in a 510(k) review due to changing interpretations and requirements. The industry desires direction and guidance as much as the agency. That said, IMDMC joins many others within industry who are seriously concerned about the formal establishment of a new "class IIb" device subset, and oppose this recommendation. IMDMC urges FDA to take a step back, and focus on providing guidance for specific higher risk device types, rather than establishing what amounts to a new PMA-like class of devices.

As currently proposed, CDRH's recommendation for a class IIb would require an amendment to the Food, Drug and Cosmetic Act. The term "class IIb" has no legal definition and implies a distinction that does not and should not exist. Congress authorized the use of special controls for class II devices and these special controls should be applied on a case-by-case basis. Congress did not give CDRH the authority or flexibility to establish another class. Absent a statutory amendment that creates and defines such a class, the proposed term has no foundation.

CDRH, however, does have the authority to publish guidance for specific device types. Indeed, CDRH already has done so on a number of occasions.[4] IMDMC strongly encourages CDRH to take this latter path to defining expectations for devices that fit within the 510(k) program but raise a higher level of risk than other devices within this classification. IMDMC anticipates that this would be a small handful of devices, and urges CDRH to formally publish this narrow list of specific, higher-risk device types to be covered by device type specific guidance documents, subject to notice and comment. In addition, as CDRH develops these guidance documents, IMDMC believes the focus should be on what evidence CDRH needs to establish substantial equivalence, and what special controls may be appropriate to mitigate the risk.

As CDRH clarifies its evidentiary and submission requirements for these specific higher-risk devices, IMDMC also encourages CDRH to consider down-classifying some devices that currently require PMA approval . Provided CDRH took a risk-based approach within the 510(k) program, which the agency appears to be doing, some higher-risk devices could fit within the 510(k) program.

An additional working group proposal related to the proposed class IIb concerns the submission of manufacturing information. The use of manufacturing information in 510(k) decision-making is generally unwarranted and unnecessary. FDA's determination of substantial equivalence is based on the intended use and technological characteristics of the device compared to a predicate. According to Section 513(i)(1)(ii)(I) of the Food, Drug and Cosmetic Act, if a device has different technological characteristics than a predicate device, "appropriate clinical or scientific data" is used to demonstrate substantial equivalence. It is not generally necessary to submit manufacturing instructions, quality control procedures, or quality system procedures to demonstrate substantial equivalence with respect to technological characteristics. Similar to periodic reporting, IMDMC encourages FDA to develop appropriate guidance on a case by case basis, describing the manufacturing information it believes is necessary to establish substantial equivalence for specific higher risk device types.

While we agree that some class II devices require clinical information, as broadly defined in the GHTF definition of "clinical data", to demonstrate substantial equivalence or post-market surveillance to monitor certain issues, we believe that it is excessive to implement such requirements on a large scale via a single guidance document for an entire proposed class II subset.

Finally, we are concerned that there is a high probability that a broadly defined "class IIb," as described by FDA, would result in less predictability in the application of appropriate regulatory requirements for the determination of substantial equivalence, especially in light of FDA's comments that "the delineation between "class IIa" and "class IIb" is meant to be a general guideline only." Therefore, we urge CDRH to avoid a "class IIa/IIb" distinction and focus on the appropriate application of additional guidance and special controls for each of the higher risk device types to be identified by FDA.

[4] Guidance for Cardiovascular Intravascular Filter 510(k) Submissions; issued November 26, 1999
Class II Special Controls Guidance Document: Root-form Endosseous Dental Implants and Endosseous Dental Implant Abutments; issued May 12, 2004

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Essential Requirement for Summaries

Lack of Clarity (in submissions) – Detailed Photos, Schematics, and Samples
Proposal: 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.

Comment: We agree with FDA that submissions should contain sufficient high-quality information to facilitate review by agency staff and that publicly available summaries of submissions should promote understanding. However, some aspects of FDA's proposals appear to establish an undue burden in light of the desired objective.

We agree with FDA that photographs can enhance understanding of a product, its function, and its relation to predicate devices. Diagrams and/or line art can also facilitate understanding. Schematics and/or detailed technical drawings, however, are considered proprietary and/or trade secret information and should not be included in publicly available 510(k) summaries. Also, the inclusion of this information in publicly-available databases would result in an undue risk to manufacturers with respect to FDA's disclosure of proprietary information.

FDA's proposal to require submission of actual devices to better understand a device during the review stage seems reasonable; however, in most cases, carefully-written descriptive information, photographs, and diagrams should be more than sufficient for a reviewer to achieve a clear understanding of the design and function of a product, especially when much of the form or function of the device may not be immediately obvious upon visual inspection. Therefore, submitting actual devices should be a recommendation, not a requirement. Furthermore, the requirement to retain products for an indefinite period of time would be a great burden to industry, particularly to manufacturers of large and/or expensive products and to manufacturers that make products with special storage conditions or that have short shelf-lives.

Incomplete Information (in submissions) – All Scientific Information
Proposal: 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.

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Comment: We agree with FDA's desire to have sufficient scientific information on a product to make well-informed decisions. However, the proposal by FDA to require 510(k) submitters to provide a list and description of all scientific evidence regarding safety and effectiveness of a device that is known to or that should be reasonably known to the submitter is unreasonably burdensome to both FDA and industry. It should be noted that the 510(k) submitters are already required to submit all relevant information (see, for example, 21 USC 360c(i)) and to certify that "[T]he submitter believes, to the best of his or her knowledge that no material fact has been omitted" (21 CFR 807.87(k)). To illustrate the burden of FDA's proposal, a recent PubMed search based on the word "laparoscopes" resulted in citation of over four thousand articles. Even without the inclusion of unpublished clinical data or pre-clinical testing, this represents an almost impossibly large volume of data to list, describe and effectively summarize, especially when much of the data may be irrelevant or redundant with regards to the particular device or to substantial equivalence. In addition, the FD C Act specifically limits the information that FDA can request to "information that is necessary to make a substantial equivalence determination," so the proposed additional data is outside the current statutory framework. For scientific/clinical information that is necessary for the determination of substantial equivalence, we recommend a summary of clinical evidence that is in line with the GHTF Study Group 5 document on Clinical Evaluation and the recent MEDDEV 2.7.1 requirement for clinical evidence, both of which narrow the scope of the relevant device specific information to a summary of *relevant* literature and *pertinent* clinical data, rather than an exhaustive list of all information.

Use of "Split Predicates" and "Multiple Predicates"

Proposal: *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, the Center should update its existing bundling guidance to clarify the distinction between multi-parameter or multiplex devices and bundled submissions.*

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.*

Disallowing the use of "split predicates" and / or 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. For this reason and those described below, IMDMC respectfully disagrees with these CDRH recommendations.

Although the use of split predicates may not be appropriate in all cases, in many instances it provides a reasonable and practical approach to establishing substantial equivalence. Rather than eliminating the use of split predicates, IMDMC believes CDRH should define *when* and *under what circumstances* use of split predicates might be appropriate. CDRH could establish guidance based on risk, and require

510(k) sponsors to justify the need for split predicates. This approach would provide both the agency and industry greater flexibility to deal with innovation as it occurs.

CDRH's proposal to prohibit more than five predicate devices as a matter of course also sets an inflexible bar that could lead to unnecessary PMA's and *de novo* requests, particularly in the case of complex multiplex devices, microarrays, sequencers and other new technologies. Rather than prohibiting more than five predicates, IMDMC proposes that the "five predicate" limit be a recommendation, not a requirement. 510(k) sponsors would have the flexibility to propose and justify additional predicates, and CDRH would have the flexibility to consider whether a review of additional predicates raises unnecessary risks.

In closing, IMDMC again commends the FDA working groups for their work as well as for their recognition of needed improvements in reviewer training and in guidance documents. We also think it important to note that there are additional factors that should be part of a comprehensive evaluation of the 510(k) process. In particular, the value of innovation, and whether the proposed changes could negatively affect such innovation, should be paramount considerations. Any increases in clearance times that result from the proposed changes will have a profound effect on the timeliness with which new technologies become available to improve patient care and outcomes in the United States. In addition, the working group reports do not appear to have considered the financial or human resources that would be needed within the agency to implement the recommended changes. Given recent agency reports of being under-resourced, and the constraints on growth – especially in the current economic climate – IMDMC believes that no changes should be made without assessing the resources which will be needed to effectively implement them, as well as identifying how the agency intends to obtain the needed resources.

Sincerely,

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DOCKET NO. FDA – 2010 – N- 0348

October 4, 2010

Dr. Jeffrey Shuren
Director
Center for Devices and Radiological Health
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Silver Spring, MD 20993

Dear Dr. Shuren:

On behalf of the members, directors and officers of the Massachusetts Medical Device Industry Council (MassMEDIC), I am forwarding these comments on the revisions proposed by the Center for Devices and Radiological Health for the 510(k) program last month. Our comment document also provides feedback on the accompanying report on the Utilization of Science in Regulatory Decision Making

MassMEDIC is a 15 year-old organization of medical device manufacturers, developers and suppliers. With over 375 members, MassMEDIC represents the second largest cluster of medical device activity in the nation. Our members -which include global medical technology companies, small-and medium sized enterprises, and start-up firms - design and manufacture some of the most innovative health care products available in the world, devices that enhance the quality of health care and improve patient outcomes.

The attached comments focus on six specific sections of the CDRH proposal, identified by MassMEDIC member companies as priorities. There are important points to be raised in other sections, but to provide concentrated input, we will limit our feedback here to the following revisions to the 510(k) program:

- Use of “Split Predicates” and “Multiple Predicates”
- Type and Level of Evidence Needed
- Unreported Device Modifications
- “Same Intended Use”
- “Different Questions of Safety and Effectiveness”
- Predicate Device Concerns

We are also forwarding comments on the provisions in the companion report on using science to guide regulatory decision-making process.

Thank you for considering our perspectives and concerns. MassMEDIC looks forward to working with policy makers at CDRH. We stand ready to provide clarification and additional information on any of the comments submitted. Please feel free to contact me at 617-414-1340 or sommer@massmedic.com.

Sincerely,

Thomas J. Sommer
President

DOCKET NO. FDA- 2010 – N - 0348

MassMEDIC Comments on Proposed 510(k) Revisions September 2010

VOLUME I – CDRH Preliminary Internal Evaluations

510(k) Working Group

Use of "Split Predicates" and "Multiple Predicates"

- Develop guidance on appropriate use of one or more than one predicate; explore possibility of explicitly disallowing the use of "split predicates" and provide training to CDRH staff
- Take additional complexity of review into account with respect to premarket performance goals
- Explore correlation of 510(k)s citing multiple predicates and above average number of MDRs

MassMEDIC Comment

MassMEDIC is encouraged by the Agency's expressed interest in developing guidance on the appropriate use of more than one predicate device. Additional clarity from the Agency on this aspect of medical device regulation is welcome. It is certainly evident from a cursory review of the 510(k) Summaries published monthly by the Agency, that firms routinely use multiple predicate devices as the basis for making substantial equivalence arguments. As a consequence, there may be considerable variability in the degree to which different firms may make reference to these multiple predicates. Indeed, it is fair to state that the use of multiple predicates has become an industry "standard practice", because it allows new products to benefit from some of the safety testing performed on cleared devices that have already undergone that testing and which have also been demonstrated to be safe and effective in post-approval use. Denying the ability to reference that body of industry knowledge and clinical evidence would force manufacturers to repeat testing of technical characteristics that have already been extensively tested.

The development of medical devices often occurs through the incorporation of functionality or technologies that may not have been available in a single predicate device. MassMEDIC members' experience is consistent with this view, and our concern is that taken to a logical extreme, the Agency's interest in disallowing the practice of referencing multiple predicates will ultimately stifle innovation, inhibit the introduction of new technologies and add to the cost of developing new devices by required repeat testing of technical characteristics that have previously been tested for safety and/or effectiveness. By disallowing comparisons to multiple predicate devices within reason, one logical consequence is that only a single device incorporating all conceivable features to be developed in the future could be utilized as a predicate, restricting manufacturers to submissions of "me-too" products. Furthermore, any introductions of new technologies or new applications for existing devices would necessarily fall into other regulatory pathways, such as the *de novo* or Pre-Market Approval pathways. It is not clear how the interest in disallowing the use of multiple predicates advances the Agency's interest

in protecting public health, if every 510(k) submission describes subject devices that only refer to a single predicate device that contains exactly the same functionality and technologies.

MassMEDIC requests that the Agency further explain its objectives regarding taking additional complexity of review with respect to premarket performance goals. As noted above, the use of multiple devices as predicates was a common practice when the premarket performance goals were initially established, and thus the time required to review 510(k) submissions with multiple predicates would have already been accounted for and should not have any significant impact on the Agency's premarket performance goals. Rather, our analysis suggests that several of the other suggested revisions, such as the distinction of Class IIA and Class IIB devices, requiring the submission of clinical data for Class IIB devices, or requiring pre-market clearance facility inspections, were not accounted for when premarket goals were established and therefore would be expected to have a greater impact on premarket performance goals than the use of multiple predicate devices.

We also request that the Agency further explain how it would perform the correlation exercise. In particular, further details associated with how the Agency would define an "above average number of MDR's" would be appropriate before implementing such an exercise. In particular, further discussion regarding how such a breakdown would be organized, how devices classified under different regulations, and subject to different intended uses, and different clinical risks would be compared, we believe would be appropriate.

Type and Level of Evidence Needed

- Develop guidance to create a sub-set of Class II devices (administrative distinction, only), known as Class II(b); require clinical information and clarify type and level of data, manufacturing information, pre-clearance inspection and potentially, expand post-market surveillance authority; risk / benefit profile to be considered in keeping device in Class II(b) or "down-grading" device to Class II(a), or vice-versa; encourage pre-submission interaction between submitters and review staff to determine appropriate information; provide training
- Continue efforts to implement unique device identifier (UDI) program
- Clarify authority to withhold clearance based on failure to comply with GMPs, e.g., for Class II(b) devices; discussion of pre-clearance inspections

MassMEDIC Comment

CDRH states that "In order to fulfill the goals of the 510(k) program, the statutory framework must be implemented and administered in a manner that both supports fully informed decision making and provides predictability. CDRH staff must have access to a sufficient level of information about 510(k) devices, as well as tools that allow for the optimal use of that information. To obtain such information without creating unnecessary delays and burden, CDRH must provide submitters with as much up-front clarity as feasible about its evidentiary expectations." (Section 5.2 Well Informed Decision Making).

CDRH also states that it is recommended that "CDRH should take steps through guidance and regulation to facilitate the efficient submission of high quality 510(k) device information, in part by clarifying and

more effectively communicating its evidentiary expectations through the creation, via guidance, of a new “Class IIb” device subset.”

MassMEDIC fully supports the goal of clarifying and communicating the expectations for evidence, but disagrees with the creation of a new device classification as a necessary implementation mechanism.

We are concerned the new Class IIb designation would add uncertainty, costs, delays and unnecessary evidentiary barriers to the 510(k) process, without providing benefits to patient care or to the health care system. We are also concerned the proposed Class IIb would drive MedTech innovation offshore to more user-friendly regulatory systems, limit patient access to exciting and beneficial new technologies and ultimately damage the leadership position of US industries in the global MedTech market.

We believe the proposed Class IIb designation, despite FDA’s claim to “represent only an administrative distinction”, will establish new classification of medical devices, beyond the terms defined in Section 513 of the Statute, and represents a “mini-PMA”. Given the current breadth of devices classified as Class II moderate risk devices, coupled with the rapid pace of technological advancement, the implementation of a Class IIb category will remain too broad and generic for FDA to effectively communicate evidentiary expectations for a heterogeneous group of devices. Therefore, the threshold can never be properly set, and is too open to arbitrary and subjective decision making.

To illustrate, CDRH states “the distinction between Class IIa and Class IIb is meant to be a general guideline only” and that for a new device it may be “not possible for CDRH to determine whether it should be included in “class IIa” or “class IIb” until it meets with the submitter”, so “the guidance should advise manufacturers of “Class IIb” devices to engage with the Center to discuss the type of evidence appropriate for their devices.”

It would appear CDRH is advocating use of the pre-IDE/IDE process for all “Class IIb” devices. Since pre-IDE has no statutory timelines, no metrics, no limit on discussion topics and is not binding, we see a risk of significant evidentiary barriers and delays, without patient or healthcare benefit. There currently exists a perception FDA defaults to conservatism in decisions and evidentiary requirements, particularly with new technologies and/or new indications. We are concerned the proposed Class IIb would provide a mandate for FDA to demand data not relevant or required to determine substantial equivalence.

MassMEDIC believes significant changes to the existing regulatory framework are unnecessary, and views this proposal as reactionary to what we believe are very few problematic decisions associated with the 510(k) process. The existing Class II designation provides FDA all the tools needed to reach a decision on device safety and effectiveness, including the right to ask for additional data, including clinical data. We recommend the following enhancements to the process to aid in the goal of clarifying and communicating expectations for evidence:

- Focus on the development and implementation of device-specific guidance that is better stratified to define evidentiary requirements based on technological features and intended use and indications for use. FDA states “The data in Table 5.7, below, suggest that 510(k)s for devices with available device-specific guidance tend to be reviewed more efficiently than those without such guidance.”

- FDA should streamline the guidance process, perhaps working more closely with Industry Groups. The goal of a streamlined guidance development process should focus on rapid

development of new guidance and rapid iteration whenever new technological advances, new indications, intended uses or device variants become known.

- Invest in training and education of review staff with regard to medical technologies, aligned with the pace of innovation from Industry. This will ensure FDA maintains a clearer understanding of technology and a better comfort level with the review thereby ensuring the appropriate level of evidence required to reach a decision on safety and effectiveness.

- Develop a communication mechanism, specific to 510(k) submissions that can be used for pre-submission discussions with FDA. This mechanism should be simpler, timely and binding compared to the current pre-IDE Meeting process.

- For new technologies and devices that do not fall within an established guidance document and also fail to meet basic evidentiary requirements of safety and effectiveness, defer to a modified de-novo approach to decide on device Classification. For Class II devices, this could then be rapidly followed by a new device-specific guidance.

Unreported Device Modifications

- Clarify types of modifications that do or do not warrant submission of a new 510(k)
- For modifications that do allow a new 510(k), clarify which modifications are eligible for Special 510(k) program
- Require each manufacturer to provide regular, periodic updates listing modifications made to its device without submission of a new 510(k) with supporting rationale

MassMEDIC Comment

MassMEDIC is particularly troubled by the proposal that manufacturers must submit an annual summary of changes to each 510(k) cleared product that DID NOT result in a new 510(k), along with the manufacturer's rationale for not requesting premarket approval. While this may seem like a harmless requirement, as manufacturers are required to document these changes and decisions already, our concern is this will open a vast new arena of second guessing, ultimately to the detriment of patient safety.

All manufacturers of electronic equipment are faced with continual component part substitution decisions for reasons of cost, obsolescence or yield that do not compromise patient safety or effectiveness. Some electro-medical companies maintain a catalog of over 50,000 component parts and assemblies to support one product line and process hundreds of engineering changes on these components in the span of one year. While most of these changes have no effect on safety or effectiveness, some changes may improve factory yield or field reliability. While such continuous improvement should be unequivocally positive, it is possible a "zero tolerance" environment to view any such change as requiring a field corrective action.

MassMEDIC believes this disclosure requirement will introduce new and significant risk into the cost/benefit decisions of sustaining engineering. Ultimately this could drive manufacturers to make fewer product improvements, which perversely would result in increased risks to patient safety.

"Same Intended Use"

- Consolidate concepts of "intended use" and "indications for use" into a single term, "intended use" and provide training to CDRH staff and industry
- Pursue statutory amendment to provide CDRH with express authority to consider "off label" use, in certain limited circumstances, when determining "off label" use

MassMEDIC Comment

MassMEDIC acknowledges that confusion exists between the terms "Intended Use" and "Indications for Use" and that industry as well as the agency have used the terms interchangeably and inconsistently. However, MassMEDIC views the confusion as a matter of inadequate training within the agency and industry. In March 8, 2001, FDA issued "Device Labeling Guidance", #G91-1 (Blue Book Memo), in which the term "intended Use" as included in the law is provided, and distinguished from the term "indications for use". Draft guidance from OIVD on Pre-IDE Information Packets, dated February 2007, distinguishes between intended use and indications for use: (1) "The intended use statement describes how the device is to be used", whereas (2) "the indications for use describes for what or for whom the device is to be used, e.g., disease, condition or patient population." By providing training to agency personnel and industry to reinforce the definitions that already exist in FDA guidance documents, MassMEDIC believes that the current level of confusion can be resolved.

Merging the two terms into "intended use" appears to be over-reaching and overlooks the fact that these two terms are distinct, have been well defined, and serve different purposes.

Combining the terms would constrain the meaning of intended use and potentially eliminate flexibility, especially in the area of allowing the agency to determine which new indications for use affect and change the intended use. There is concern that combining the two terms will increase the number of Not Substantially Equivalent determinations, resulting in unnecessary PMA's or 510(k) de novo applications, both of which could delay safe and effective product from reaching the market. MassMEDIC believes the confusion could be reduced or eliminated if the agency would reinforce the existing definitions for each term as it relates to substantial equivalence.

"Different Questions of Safety and Effectiveness"

- Reconcile language in 510(k) flowchart with language in statute, 513(i), i.e., different technological characteristics, and different questions of safety and effectiveness; revise existing guidance to provide clear criteria for identifying different questions of safety and effectiveness, and develop core list of technological changes; and provide training for CDRH staff and industry.

MassMEDIC Comment

It is not evident that incorporating the specific language of the FDC Act would provide clearer criteria for the current 510(k) "Substantial Equivalence" decision-making process flowchart. In fact, modifying the flowchart may lead to additional confusion in the decision-making process. Currently, the value of the

rigor behind the 510(k) review process is 1) presenting and discussing technological characteristics and 2) examining the safety and effectiveness profile when there are new characteristics and safety questions raised. We believe the current flowchart systematically and satisfactorily leads the reviewers to consider how any device modifications, from its predicate(s), may lead to new questions concerning safety and effectiveness. Thus, we have confidence that the current flowchart leads to, and results in, meeting the same definition of "Substantial Equivalence" as stated in the FDC Act.

In regards to revising existing guidance to provide clearer criteria for identifying "different questions of safety and effectiveness", it is unclear which specific guidance the 510(k) Working Group is referencing. Additionally, more information is necessary to understand and digest the specifics of the core list. We applaud the working group's effort with these recommendations but believe implementing this high level of information through guidance and core lists will be extremely difficult to apply to all types of devices unless this information is specific to device type, product code, and intended use. However, if CDRH were able to generate and revise informative specific guidance for each device type in a timely manner this would enable the industry to utilize and streamline these resources for clarity and input. Ultimately, this may be beneficial if this process is able to improve communication between CDRH and industry and help reduce review times and agency costs

Providing training for CDRH staff and industry is always well warranted, especially if the type of training is uniform and division specific. We highly recommend routine and standardized staff and industry training if this can be accomplished at the division and branch level.

Predicate Device Concerns

- Predicate Quality: Develop guidance on when a device should no longer be available for use as a predicate due to safety and/or effectiveness concerns
- Rescission Authority: issue a regulation to define the scope, grounds, and appropriate procedures to fully or partially rescind a 510(k) clearance.

MassMEDIC Comment

CDRH proposes developing guidance on when a device should no longer be available for use as a predicate due to safety and/or effectiveness concerns.

This recommendation raises several questions: How will these new authoritative actions affect other products already cleared which have used the questionable/rescinded predicate device(s) in their submission? Will this mean that any other device which has been cleared using the predicate would also become unavailable as a predicate, or require resubmission with another predicate?

Except in the situation where a new device uses a previous version of the same device as its predicate, the safety and effectiveness of one device should not have any impact on the safety and effectiveness of another device due to identified predicate device issues.

These new proposals appear to go beyond the current FDA authoritative actions, (i.e. Warning Letters followed by further legal actions) when a device manufacturer fails to meet the regulatory obligations and enacted statutes. Based on the current regulatory actions available to FDA we feel that the "Predicate Quality" and "Rescission Authority" processes are not necessary. These new actions would

only incur additional time and effort for industry as we compile new submissions and/or monitor our current marketed device activities.

CDRH also recommends issuing a regulation that defines the scope, grounds, and appropriate procedures to fully or partially rescind a 510(k) clearance.

Again, MassMEDIC believes such a regulation would raise several questions: How will such a regulation impact devices which used a removed predicate device as its predicate post clearance? How does that affect cleared devices already in the marketplace should its predicate no longer be usable? Does it mean a re-submission will be required or a rescission?

VOLUME II – CDRH Preliminary Internal Evaluations

Task Force on the Utilization of Science in Regulatory Decision Making

In reviewing the accompany report on the use of science in the regulatory decision making process at CDRH, MassMEDIC wishes to strongly endorse three recommendations in particular:

Applying a Predictable Approach to Determine the Appropriate Response to New Science

MassMEDIC especially supports the recommendation that CDRH promptly communicates current or evolving thinking to all affected parties on incorporating new science into regulatory decisions. The notion of establishing a "Notice to Industry" template for informing industry of changes in regulatory expectations and the rationale for such changes would provide great clarity to manufacturers and is strongly endorsed.

Leveraging External Scientific Expertise

We applaud CDRH for taking steps to seek independent external scientific expertise to support on-going education for its staff. Web-based sources of information as well as site visits and collaborations with academic research institutions will be helpful in assessing the many new technologies deployed in medical devices. MassMEDIC wishes to assist CDRH in identifying potential sources of scientific and technological expertise.

Promoting Flexible Staffing Policies to Alleviate Peak Workload Demands

MassMEDIC backs the recommendation that would allow CDRH to quickly allow for the swift formation of *ad hoc* review teams from various divisions to deal efficiently with unexpected surges in workload. This flexibility in staffing would keep the review process on track, insuring that new medical technologies would be made available to patients and health care providers in a timely manner.

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Re: Request for Comment; Center for Device 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
DOCID: FDA-2010-N-0348
Date Submitted: September 30, 2010
Submitted by: Alliance for Aging Research

Thank you for the opportunity to provide feedback on the FDA's examination of the 510(k) process for medical devices and the recommendations contained in the Working Group's preliminary report. The Alliance for Aging Research applauds the agency for taking on this challenging task and we are pleased with many of the recommendations set forth in the preliminary report. For example, drafting and issuing more quality guidance for product developers, can improve the process by making it more predictable and consistent, thus encouraging innovation to the benefit of patients. Enhancement of training, professional development of the agency staff is a key piece of providing greater assurance to the safety and effectiveness of approved devices. We believe the idea of applying special requirements to a small subset of devices laid out in the preliminary report would be a positive change and possibly reduce the need for more sweeping reforms called for in the bulk of the report, with proper implementation.

However, the Alliance does have some concerns with the report that we hope will be addressed before any recommendations are finalized. As part of the report's section on "A Rational, Well-Defined and Consistently Interpreted Review Standard, " redefinition of the term "substantial equivalence," new limitations on acceptable reference products, and the removal of separate classification of "intended use" and "indications for use" have the potential to make approval more time-consuming, impacting new product development and timely patient access. There may also be unintended consequences on patient access to new technologies as a result of the recommendation in this section centered around new authorities to consider potential off-label use when determining the "intended use" of a new device under the 510(k) process. We fear that withholding approval of a new device because the agency believes it may be used off-label, could prevent technologies from reaching the intended patient population.

As an organization that actively advocates for proper resourcing of the agency to speed patient access to new therapies and technologies, the Alliance is concerned that the recommendations in the report would represent a huge diversion of FDA staff, time and funding at a time when the agency is just recovering from years of budget shortfalls. We are also concerned that requiring some technologies that appropriately go through the 510(k) process to now go through the Premarket Approval (PMA) process as highlighted in the report can lead to increased research costs and delays in patient access. We strongly urge FDA to consider limiting changes to the 510(k) process to where they are clearly needed.

The Alliance for Aging Research is the nation's leading not-for-profit organization for advancing a broad agenda of scientific and medical research in human aging. Our organization supports policies to help improve the health and independence of Americans as they age. We hope that the needs of patients who struggle with chronic and disabling conditions remain in the forefront of the agency's consideration of changes to its 510(k) review process. Recognizing the important role medical devices play in many aspects of life for older Americans, we would welcome the opportunity to provide additional information to FDA as the Working Group's recommendation near finalization.

Thank you for your consideration of these comments.

Sincerely,

Daniel P. Perry
President and CEO

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October 4, 2010

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

Submitted electronically and via FedEx

RE: Boston Scientific Corporation Comments to Docket No. FDA-2010-N-0348 CDRH Preliminary Evaluations, 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/Madam:

Boston Scientific Corporation appreciates the opportunity to submit these comments in response to the Center for Devices and Radiological Health (CDRH) Preliminary Internal Evaluations, 510(k) Working Group's Preliminary Report and Recommendations, and the Task Force on the Utilization of Science in Regulatory Decision Making (the "CDRH recommendations") released August 4, 2010.

Boston Scientific is a worldwide developer, manufacturer and marketer of medical devices. For more than 30 years, Boston Scientific has advanced the practice of less-invasive medicine by providing a broad and deep portfolio of innovative products, technologies and services across a wide range of medical specialties. The Company's products help physicians and other medical professionals improve their patients' quality of life by providing safe and effective alternatives to surgery.

Boston Scientific commends FDA for taking a critical look at the 510(k) program and for identifying areas for improvement within CDRH. We recognize that many of the CDRH recommendations will benefit both industry and the Agency. The recommendations relating to enhancement of training for CDRH review staff, additional clarification for certain terms related to the 510(k) program, and streamlining the guidance and de novo 510(k) processes should improve the consistency and predictability of the 510(k) program. We offer our assistance, as