Alliance
FOR AGING RESEARCH

www.agingresearch.org

2021 K Street, NW | Suite 305 | Washington, DC 20006
T 202.293.2856 | F 202.785.8574

**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

**Boston Scientific Corporation – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0032**

Boston Scientific Corporation
One Boston Scientific Place
Natick, MA 01760-1537

Telephone: 508-650-8000
www.bostonscientific.com

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

appropriate, in developing new training programs and guidance documents and request that internal CDRH training programs on regulatory processes also be made available to industry. Consistent training for both CDRH and industry will promote mutual understanding and application of the regulatory requirements, ultimately benefiting patients by enabling timely approvals of safe and effective medical devices, diagnostics, and combination products.

Boston Scientific is a member of both the Advanced Medical Technology Association (AdvaMed) and the Medical Device Manufacturers Association (MDMA), and we endorse the positions articulated in their comments submitted to the FDA docket in response to the CDRH recommendations. However, we would also like to take this opportunity to provide our own comments on specific areas of concern to Boston Scientific. We recognize that the CDRH recommendations are preliminary and lack the detail necessary for a full impact assessment. Boston Scientific looks forward to providing more detailed input once CDRH has reviewed all comments and determined which recommendations to move forward with more detailed proposals.

***The 510(k) Working Group recommends that CDRH revise existing guidance to consolidate the concepts of "indications for use" and "intended use" into a single term, "intended use".***

Boston Scientific supports the need to clarify the definitions of and provide additional guidance for the appropriate uses of the two terms, *intended use* and *indications for use*. However, Boston Scientific does not support consolidating the two terms into the single term, *intended use*.

The terms *intended use* and *indications for use* have distinctly different meanings and are both integral to the 510(k) program. The FDA *Guidance on the CDRH Premarket Notification Review Program 6/30/96 (510(k) Memorandum #K86-3)* clearly delineates the differences between these terms. The guidance states, "While a new device must have the same intended use as a predicate device in order to be SE, the Center does not require that a new device be labeled with precise therapeutic or diagnostic statements identical to those that appear on predicate device labeling in order for the new device to have the same intended use. Label statements may vary. Certain elements of a predicate device's labeled indication may not be critical to its intended therapeutic, diagnostic, prosthetic, surgical, etc., use . . .. Thus, a new device with the same intended use as a predicate device may have different specific indication statements, and, as long as these label indications do not introduce questions about safety or effectiveness different from those that were posed by the predicate device's intended use, the new device may be found SE."

*Intended Use* is a statement of what the device does or the claimed purpose of the device. As established by law, a new device evaluated under the 510(k) regulations must have the same intended use as the named predicate device(s) in order to be found substantially equivalent. By

comparison, *indications for use* may set forth specific information to further define, for example, different use environments, patient populations, disease states, or methods of use. A new device with different indications for use can still be found substantially equivalent to a predicate device as long as the intended uses are the same and the differences in indications for use do not introduce different questions of safety or effectiveness (see *K86-3*). By consolidating the two terms into one, this distinction would be lost with the result that any change to a device's indications for use, even if the change did not raise different questions of safety or effectiveness, would render that device not substantially equivalent (NSE). This situation would be the antithesis of one of the principles set forth for the 510(k) program in the K86-3 Memorandum, "If substantial equivalence were judged too narrowly, the marketing of devices that would benefit the public would be delayed; the device industry would be unnecessarily exposed to the greater burdens of premarket approval; new devices would not be properly classified; and new manufacturers of pre-Amendments type devices would not have marketing equity."

Boston Scientific concludes that the distinctions between a device's *intended use and indications for use* are important for successful application of the 510(k) program and its principles. The two terms should remain discrete, but with clear definitions, guidance, and training. We suggest that the liberal use of examples will be beneficial to clearly explaining the differences between these two terms as well as the threshold for when different indications for use raise different questions of safety or effectiveness and would render a device NSE.

***The 510(k) Working Group recommends that CDRH explore the possibility of pursuing a statutory amendment to section 513(i)(1)(E) of the Federal Food, Drug and Cosmetic Act (21USC§360c(i)(1)(E)) 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. Such circumstances would include the availability of compelling evidence that the primary use of the marketed device will be off label.***

With the enactment of FDAMA, Congress provided clear direction and limits on how the Agency may address potential off label use of devices undergoing 510(k) review. Congress was clear that CDRH could not withhold 510(k) clearance on the basis that the device might be used off-label. Instead, the Food Drug  Cosmetic Act (FDCA) was revised to give CDRH the authority to issue a "Substantial Equivalence with Limitation(s)" decision and require a warning statement in the device labeling if CDRH determines there is a reasonable likelihood that the device will be used off-label and that the off-label use could cause harm. Thus, Congress upheld two longstanding principles that: 1) the FDCA cannot be used to regulate off-label use by a healthcare practitioner ("[n]othing in this Act shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a

patient for any condition or disease within a legitimate healthcare practitioner-patient relationship (see FDCA  906)); and 2) that a device s intended use is determined by the objective intent of the persons legally responsible for the labeling of devices (see 21 CFR 801.4). As long as the intended use put forth in the 510(k) is bona fide for the device, 510(k) clearance should not be withheld because healthcare practitioners may use the device off-label. The current SE with Limitation(s) program strikes an appropriate balance as it does not interfere with the practice of medicine, but does convey important information about the status of a potential off-label use for the device or diagnostic.

Since 513(i)(1)(E) was implemented via FDA guidance in 1998, a total of 306 SE With Limitation(s) decisions have been issued through July of 2010 (see CDRH Releasable 510(k) Database at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm). This total includes limitations related to potential off-label use as well as for other reasons, such as warnings related to potential adverse events. In the same time period, nearly 48,000 510(k)s were found to be substantially equivalent and cleared for marketing. Therefore, the SE with Limitation(s) decisions represent less than 0.6% of the total SE decisions. These data indicate that concerns with potential off-label use arise in a very small percentage of 510(k) decisions and call into question the need to change the current Congressional framework and FDA practices for handling potential off-label use of 510(k) cleared devices and diagnostics.

***The 510(k) Working Group recommends that CDRH consider developing guidance on when a device should no longer be available for use as a predicate because of safety and/or effectiveness concerns. It is expected that such a finding would be an uncommon occurrence.***

Boston Scientific welcomes CDRH guidance documents that assist CDRH reviewers and industry to better understand and comply with applicable FDA regulations. However, such guidance must be in support of current law and regulation, and not be in lieu of formal process for creating new regulatory requirements.

With respect to the issue of appropriate predicate devices, Section 513(i)(2) of the Federal Food Drug and Cosmetic Act already establishes that, A device may not be found to be substantially equivalent to a predicate device that has been removed from the market at the initiative of the Secretary or that has been determined to be misbranded or adulterated by a judicial order (see also 21 CFR 801.100)(b)(3)). The law ties the criteria for when a device can no longer be used as a predicate to situations in which the device has been removed from the market via established administrative or judicial process. While additional guidance on this process may be helpful, Boston Scientific is concerned that the recommendation as stated implies an attempt to broaden the law by lowering the threshold currently established in 513(i)(2).

Removal of a legally marketed device as a lawful predicate is a serious issue and one with significant downstream consequences, raising questions about the marketing status of devices that had previously used the removed device as a predicate but may not have the same safety or effectiveness concerns. Boston Scientific urges CDRH to restrict such actions to circumstances contemplated by the current law and, even then, only when necessary to protect the public health.

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

As stated in the CDRH recommendations, the Agency already has "inherent authority to reconsider their decisions in certain circumstances, such as where there has been fraud or error, and to rectify their mistakes." Boston Scientific supports a regulation that would provide clear criteria and process, including notice and an opportunity for hearing, for CDRH to exercise this inherent authority with respect to 510(k) decisions. However, Boston Scientific believes that full or partial rescission of a 510(k) clearance should only be available as an Agency remedy if it is determined that a 510(k) Notification had included fraudulent information relied on for the SE decision or omitted material information that, had it been included in the submission, would have resulted in an NSE decision. Absent fraud or omission, 510(k) rescission should not be used as a way to subsequently address device safety or efficacy concerns. If safety or efficacy concerns rise to the level of serious risk to public health, FDA should use its recall authority under 21 CFR 810, or other available enforcement tools such as injunction or seizure, to remove unsafe devices from the market.

As an accompaniment to any new regulation, FDA should provide detailed guidance as to how a rescinded 510(k) clearance, due to fraud or omission, will affect legally marketed devices that used the device subject to the rescission as a predicate. A 510(k) rescission could set off a cascade of events that could call into question the clearance of every product that identified the rescinded device as a predicate, as well as all subsequent devices that used those products as predicates, creating the potential for safe, beneficial devices to be removed from the market.

***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".***

Boston Scientific supports the proposal that FDA develop guidance on the appropriate use of multiple predicates. However, Boston Scientific does not agree that FDA should explicitly disallow all use of "split predicates". Split predicates, or the use of one predicate for the

intended use and another for new technological characteristics, may be appropriate in certain circumstances.

Per the 510(k) regulations, a device with the same intended use can be found substantially equivalent to a device with different technological characteristics as long as the information submitted in the 510(k) demonstrates that the different technological characteristics do not raise different questions of safety or effectiveness and the new device is at least as safe and effective as the predicate device. The need for split predicates may arise when a new device has the same intended use as a legally marketed predicate, but different technological characteristics. A second device, previously cleared by 510(k) may be useful to show that the technical characteristics of the new device do not raise different questions of safety or effectiveness, even if the second device has a different intended use. A hypothetical example could be the case in which a new device has the same intended use as a legally marketed predicate but is made of a different material. A second device made of the same material as the new device and used in the same location in the body but for a different intended use, may be appropriate to answer questions about the new material. A 510(k) that uses split predicates must still satisfy the substantial equivalence criteria. If FDA believes that the information and test results presented in the 510(k) do not support a substantial equivalence determination and the device is in fact novel, FDA has the authority to find the new device NSE, and the sponsor has the option of the de novo classification process. Boston Scientific recommends that split predicates remain an option for industry, but that the Agency develop clear guidance to define the terms "multiple predicates" and "split predicates," the differences between the two, and the circumstances under which their use is acceptable.

***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 make 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).***

Boston Scientific does not support the proposal as stated. Additional clarity is needed to identify the types of modifications considered for the scope of this recommendation and the benefit the information would provide.

The FDA guidance document, "*Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)*" has been in existence since January 1997, providing clear guidance as to the types of changes that can be made to a 510(k) cleared device without needing to file a new 510(k). The policies and procedures in this guidance were adopted by FDA because the Agency understood that many changes are made to devices for a variety of reasons that do not significantly affect the safety or effectiveness of the device and do not warrant FDA review or pre-approval. Manufacturers are required to have procedures in place to assess each individual

change for 510(k) submission requirements and internally document the rationale for each change that is determined to not require a new 510(k) in accordance with the FDA criteria. In addition, each change must be assessed collectively with all prior changes made since the 510(k) clearance to determine if the threshold for filing a new 510(k) has been triggered. FDA can audit a company's internal system and documentation of decisions made with respect to such changes to 510(k) cleared devices during quality system inspections.

It is not clear what additional benefit or protection to public health would be gained by requiring manufacturers to submit periodic reports to FDA documenting all changes not submitted in new 510(k)s. Given the thousands of devices and diagnostics that are currently on the market via the 510(k) process and the fact that such devices may undergo minor changes every year, the volume of data generated by this requirement would be significant and potentially overwhelming for current CDRH resources. While companies are already required to keep internal documentation of all changes and the associated rationale for those not submitted in a new 510(k), the work to compile all of this information into a coherent report each year would also be significant. Boston Scientific requests that CDRH consider this recommendation very carefully and not move forward with implementation unless and until the need for these periodic reports is clearly established, with evidence that such reporting is needed to protect public health, and sufficient CDRH resources are in place to review and make appropriate use of the information in the reports.

***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.***

Boston Scientific does not support this recommendation as it is an overly broad requirement to meet the 510(k) standard of Substantial Equivalence.

Under current law and regulation, a 510(k) Premarket Notification must include all information that is material to the decision of Substantial Equivalence. Every 510(k) must include a signed Truthful and Accurate Certification by which the submitter certifies that all information in the 510(k) is truthful and accurate and that no material fact has been omitted. If the CDRH reviewer believes that there is insufficient information in a 510(k) to arrive at a decision, the reviewer has the option to issue a Request for Additional Information. If CDRH determines that a 510(k) includes false information or omits material information, then administrative and enforcement remedies are available. If CDRH has concerns that industry is not complying with the data requirements for 510(k), then perhaps better guidance, training, and communication will improve the quality of 510(k) submissions.

The CDRH recommendation as written would significantly broaden the current data standard for 510(k) to include "all scientific information regarding the safety and/or effectiveness of the device known to or that should be reasonably known to the submitter," and would require that this broad array of information be included in the initial submission, even if the information is not material to the Substantial Equivalence decision. This recommendation moves the data requirements for 510(k) into the realm of those required for PMA with the associated standard of "reasonable assurance of safety and effectiveness."

If CDRH has determined that certain types of information, necessary for an SE decision, are absent from the required contents of a 510(k) Premarket Notification, an alternative approach would be to update 21 CFR 807.87 to specify the additional necessary information. This should be done through the notice and comment process enabling stakeholders the opportunity to comment on the specific recommended changes.

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

Boston Scientific supports the goal of CDRH to provide clarity and predictability as to the types of devices in Class II for which clinical information may be necessary to support a substantial equivalence decision along with the rationale behind this need for each device type. Transparency and predictability to data requirements is essential for industry to plan for premarket testing requirements, timelines, and financial support needed to bring products to market. However, Boston Scientific is very concerned that this CDRH recommendation has raised the potential for manufacturing information and postmarket evaluations to be routinely required for certain Class II devices regulated by 510(k). Manufacturing information may be requested by CDRH if it is necessary to reach a substantial equivalence decision, but the need for this type of information in a 510k) should be rare. In addition, CDRH currently has the authority to require a manufacturer to conduct postmarket surveillance of a Class II device under Section 522 of the FDCA, but postmarket evaluation is not typically required to support a substantial equivalence decision. If the risk profile for a device is so unknown as to require this type of information, then the device may be more appropriately evaluated under the PMA regulations.

The increased clarity and predictability at the heart of this recommendation can be achieved if CDRH makes public a list of device types for which clinical information has been routinely required along with the associated rationale. This information would put manufacturers on notice that there may be increased requirements for a particular device and why, and enable manufacturers to initiate discussions with CDRH early in the device development process.

Boston Scientific does not support the creation of a new subclass, Class IIb. Defining a new subclass implies that products in this subclass will be regulated differently. Creating a new subclass may also make it difficult to reduce the requirements on device types once sufficient information is known about the device type to no longer warrant enhanced data requirements in order to reach a substantial equivalence decision and protect the public health.

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

Boston Scientific does not support the above recommendations because, with the exception of design controls, compliance with FDA's good manufacturing procedures (GMP) is not a pre-clearance requirement for a finding of substantial equivalence. 510(k) is a classification process, and a finding of substantial equivalence is based on comparison of intended use and technological characteristics to a predicate device, not on whether the device is manufactured in compliance with GMPs. In many instances, the commercial manufacturing facility for the device may not be operational at the time of clearance and, therefore, a pre-clearance inspection would not be possible.

FDA has considerable authority to inspect medical device manufacturers and to withhold distribution, or mandate a recall per 21 CFR 810, of any devices found to be adulterated for failure to comply with good manufacturing requirements if such a failure presents a serious risk to human health. However, withholding 510(k) clearance is not an appropriate sanction in such cases for the reasons stated above.

***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 with in a reasonable period of time after clearance, and also to provide regular, periodic updates to device labeling, potentially as part of annual registration and listing or through another structured electronic collection mechanism. If CDRH adopts this approach, updated labeling should be posted as promptly as feasible on the Center's public 510(k) database after such labeling has been screened by Center staff to check for consistency with the device clearance.***

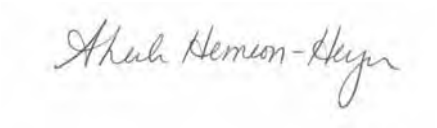
Current regulations require that each owner or operator required to register with FDA "maintain a historical file containing the labeling and advertisements in use on the date of initial listing" as well as "any labeling or advertisements in which a material change has been made any-time after initial listing" (see 21 CFR 807.31(a) and (b)). In addition, the owner or operator must be prepared to submit such labeling and advertising information to FDA upon request as specified in 21 CFR 807.31(e). Finally, FDA has authority to inspect all labeling and advertising materials to assure that they are being maintained in accordance with the listing requirements and that the information therein is in accordance with the intended use, indications for use, and claims as cleared by FDA.

Boston Scientific is unclear as to what additional benefit would be gained by requiring manufacturers to electronically submit all final device labeling, and periodic updates of device labeling, for 510(k) cleared devices. Given the thousands of 510(k) cleared devices on the market, this would create a significant amount of additional work for CDRH to review and process each labeling submission. Boston Scientific urges CDRH to consider this recommendation very carefully before implementing this broad requirement in light of the current authority already provided in 21 CFR 807.31 to request labeling and advertising as needed on a case-by-case basis.

Boston Scientific also does not understand the rationale for the CDRH recommendation to post all device labeling on its public 510(k) database. It is the manufacturer's responsibility to provide appropriate labeling to the appropriate end users and to assure that updated labeling is similarly distributed. Copies of labeling are available upon request or may be available electronically on a company website, targeted at the appropriate end users. The benefit for making all labeling publicly available for anyone to access on the CDRH database is unclear, especially for prescription devices when the labeling is intended for a licensed practitioner.

Boston Scientific would like to thank FDA for the opportunity to provide comments on the CDRH recommendations. We look forward to providing additional input as the implementation plans for the chosen recommendations are put forth for further notice and comment. We also offer our assistance to work together with FDA to assure robust, predictable processes that foster innovation, protect public health, and enable the delivery of safe and effective medical devices and diagnostics to patients around the world.

Respectfully Submitted,



Sheila Hemeon-Heyer
Vice President, Global Regulatory Affairs
Boston Scientific Corporation

**ICU Medical, Inc – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0033**

ICU Medical, Inc.

October 4, 2010

Dr. Jeffrey Shuren
Center for Devices and Radiological Health
Food and Drug Administration
Division of Dockets Management (HFA-305)
http://www.regulations.gov

**Re: Docket No. FDA-2010-N-0348; August 2010 CDRH Preliminary Internal Evaluations – Volume I (510(K) Working Group Preliminary Report And Recommendations) and Volume II (Task Force On The Utilization Of Science In Regulatory Decision Making Preliminary Report And Recommendations)**

Dear Dr. Shuren,

Thank you for the opportunity to comment on the "CDRH Preliminary Internal Evaluations," Volumes I ("510(k) Working Group Preliminary Report and Recommendations") and II ("Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations") ("Working Group Recommendations" and "Task Force Recommendations," respectively).

ICU Medical, Inc. constantly makes technological innovations to its product offerings with the goal of improving patient outcomes. While ICU recognizes the Center's important role in ensuring the effectiveness and safety of new and modified medical devices, there exists a competing concern that technological advancements not be impaired by regulatory requirements rendering such advancements unduly expensive or burdensome, or delaying the implementation of these more efficacious devices. ICU's attached comments focus on the balance between these issues and on increasing Industry's input with respect to new guidelines, new technology, and scientific studies.

ICU appreciates the efforts of the Working Group and the Task Force, as well as the Center, in undertaking a thorough review of the 510(k) process and appreciates your consideration of ICU Medical's comments.

Respectfully,

Alison D. Burcar,
Vice President of Product Development

**1. Working Group recommendations regarding combining "indications for use" and "intended use."**

On page 7 of the Overview of Findings and Recommendations ("Overview") and in Section 5.1.1.1, page 45, of the Working Group Recommendations, the 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." The Working Group, then recommends, however, that the "CDRH carefully consider what characteristics should be included under the term 'intended use,' so that modifications that are currently considered to be only changes in 'indications for use' and that CDRH determines do not constitute a new 'intended use,' are not in the future necessarily construed as changes in 'intended use' merely because of a change in semantics."

On page 7 of the Overview and in Section 5.1.1.1, page 49, of the Working Group Recommendations, the Working Group recommends that "CDRH develop or revise existing guidance to clearly identify the characteristics that should be included in the concept of 'intended use.'"

The recommendations that CDRH carefully consider what characteristics fall within the definition of "intended use" and develop guidelines to "clearly identify" such characteristics are critical to the success of the proposed consolidation of the terms "intended use" and "indications for use." Working with Industry, the CDRH should develop specific guidelines for what labeling changes can be made without the filing of a new 510(k), and such guidelines should not expand filing requirements beyond the current practice. For example, a labeling change to the product's directions for use that clarifies the procedure for using such product should not trigger the need for a new 510(k) filing.

**2. Working Group recommendations regarding creation of a new "class IIb" category.**

On page 10 of the Overview and in Section 5.2.1, page 67, of the Working Group Recommendations, the Working Group recommends "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."

On page 11 of the Overview and in Section 5.2.1.3, page 76, the Working Group recommends "CDRH develop guidance defining a subset of class II devices, called 'class IIb' devices, for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting would *typically* be necessary to support a substantial equivalence determination." The Working Group notes: "Determining what device types might be included in 'class IIb' would require further consideration. Potential candidates may include some implantable, life-sustaining devices, and/or life-supporting devices, which present greater risks than other class II device types. A specific type of device may be removed from the 'class IIb' subset as its technology and its risk/benefit profile in clinical practice become better

understood.

This proposal causes significant concern about its potential to significantly increase the burden on sponsors of a large class of *moderate* risk devices. If, on the one hand, the implementation of this proposal results in (a) a narrowly and clearly drawn subclass IIb and (b) better early communication between FDA and product sponsors regarding the scope of FDA's evidentiary expectations for 510(k) clearance of such devices, then this proposal seems appropriate and useful.

However, if subclass IIb is either broadly or vaguely defined, the device industry, and therefore device innovation, will suffer as a result of added burden or uncertainty. Further, there are indications elsewhere in the Working Group recommendations that the creation of subclass IIb might become a vehicle to increase the requirements imposed on Industry (for example, the suggestions in section 5.2.1.1 of requiring manufacturers to provide "periodic updates to the Center listing any modifications," commencing with class IIb devices, and in section 5.2.1.3 of requiring postmarket studies as part of the class IIb guidance). Such new requirements would create added burdens on Industry and would impede the development of useful innovations because the expense of such postmarket studies, which often cost as much as $300,000-$500,000, may be difficult to justify if the result of the postmarket study might ultimately derail or delay final 510(k) clearance. Further, it would appear that adding new requirements to the new subclass would in effect create a fourth class of devices, exceeding the FDA's authority.

**3. Working Group recommendations regarding device modifications**

On page 10 of the Overview and in Section 5.2.1.1, page 68, of the Working Group Recommendations, the Working Group recommends "CDRH revise existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k), and, for those modifications that do warrant a new 510(k), what modifications are eligible for a Special 510(k)."

On page 10 of the Overview and in Section and 5.2.1.1, page 68, the Working Group recommends "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."

Clarification of which device modifications trigger the need for a new 510(k), and which modifications are eligible for a Special 510(k), would help manufacturers with compliance. However, requiring Industry to constantly update the Center on all device modifications and justify why such modifications do not require a new 510(k), will significantly increase the burden on both Industry and on the Center, without any demonstrated need for such a change.

The Working Group notes that "in some situations, a manufacturer may make several successive minor modifications, none of which would warrant a new 510(k) individually, but which, taken together, could significantly affect safety and/or effectiveness." However, where a modification, when analyzed collectively with all other changes since the last 510(k) clearance, could significantly affect the safety or effectiveness of the device, the manufacturer has an existing obligation to file a new 510(k). The enforcement of the existing regulation would solve the stated problem without increasing the burden on the industry members who already comply.

**4. Working Group recommendations regarding scientific information**

On page 11 of the Overview and in Section 5.2.1.2, page 74, of the Working Group Recommendations, the Working Group recommends "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."

While this proposal would increase the information available to CDRH in the review process, it fails to address the issue of the reliability of such scientific information. There has been a proliferation of research for hire in the Industry, where studies are performed using scientifically invalid protocols, often by researchers with an undisclosed interest in the outcome. These studies often pit the "new device" against a competitor's existing device and are set up in a way to ensure the new device outperforms the competitor's device. For example, a study in a peer-reviewed journal tested the ability of chemotherapy transfer devices to contain airborne contaminants, using titanium tetrachloride (which forms "smoke" when exposed to moisture in the air) as the indicator. The lead authors of this study, who were on the Scientific Advisory Board for the "winning" device, did not reveal that TiCl4 destroys the silicone seal in the comparative ICU product tested but does not damage the "winning" device, as it has no silicone components. In effect, TiC14, which has no real similarities to chemotherapy drugs, was used to intentionally make a product "fail" that otherwise is compatible with agents for which it is intended to interact. The supposedly "scientific" information was therefore false and misleading.

Several measures can, and should, be taken to minimize reliance on invalid studies. First, the Center, with input from Industry and the scientific community, should adopt a protocol approval process for all scientific work used by the sponsor to support its device. Second, the device sponsor should be required to list all financial relationships between it and the authors of any supporting studies that it submits. Third, the Center should notify the maker of any competitive device tested in such studies of its intent to review and potentially rely on such study and allow that interested party to comment on the validity of the testing performed.

**5. Working Group recommendations regarding postmarket authorities**

On page 12 of the Overview and in Section 5.2.1.3, page 79, of the Working Group Recommendations, the Working Group recommends "CDRH explore greater use of its postmarket authorities, and potentially seek greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices."

Depending on the required parameters, postmarket surveillance can have a prohibitively high cost which could prevent new devices from coming to market or could lead manufacturers of useful niche devices to abandon such devices. For example, the FDA has recently required postmarket surveillance of positive displacement needleless IV connectors. Despite that many hospitals have found the use of positive displacement connectors to be beneficial in particular circumstances, this requirement may result in many, if not all, of these positive displacement devices being taken off the market. First, the newly required postmarket studies create an enormous expense not justified for a low-cost, niche device. Further, manufacturers may be unable to find facilities willing to participate in such studies in light of the FDA's publicly stated, but as of now unconfirmed, concern about the possible health risks associated with these devices when there are ten alternative needleless connectors available.

In contrast, if rather than requiring postmarket studies for extended periods following the general rollout of a product, the Center were to develop specific guidelines, with Industry input, for a beta testing protocol and expedited review of the beta testing results, safe and effective products could be introduced to the market in an efficient and cost effective manner. Such focused efficacy trials would have an advantage over broader clinical trials in that safety issues could be more quickly identified with fewer patients affected.

**6. Working Group recommendations regarding submission of labeling**

On pages 13-14 of the Overview and in Section 5.2.2.2, page 86, of the Working Group Recommendations, the Working Group recommends "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."

This recommendation, particularly in light of the Task Force's recommendation regarding a label repository discussed below, should have a positive impact by creating greater transparency at minimal cost.

**7. Task Force recommendations regarding scientific expertise and information**

On page 8 of the Overview of Findings and Recommendations ("Overview") and in Section 4.1.3, page 26, of the Task Force Recommendations, the Task Force recommends that "CDRH should improve its mechanisms for leveraging external scientific expertise."

On page 8 of the Overview and in Section 4.2.1, page 29, of the Task Force Recommendations, the Task Force recommends that "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."

As part of these efforts recommended by the Task Force, the Center should include the wealth of scientific expertise available within the medical device industry in its outreach, and seek Industry input as early in the decision-making process as possible to avoid decisions based on studies that lack scientific validity. For example, ICU Medical has been designing and manufacturing Needleless connectors for two decades and produces the largest volume of these devices in the United States today. The ICU Medical technical teams are very expert at issues surrounding "Positive Displacement" or "Split Septum," just as other manufacturers of connectors will also have significant insight into the issues relating to these devices. When evaluating scientific information or protocols submitted by product sponsors, the agency should adopt a policy of obtaining a "peer review" from manufacturers of similar devices.

On page 30 of the Task Force Recommendations, the Task Force sets out a four-tiered "proposed conceptual framework" consisting of: Step 1 Detection; Step 2 Escalation; Step 3 Deliberation; and Step 4 Action. The options for Step 4 Action include public communication. However, the Center should be communicating with Industry and obtaining its input as early in the process as possible, such as at Step 2 Escalation, so that such input is available at the deliberation stage.

**8. Task Force recommendations regarding Industry submitted guidance proposals**

On page 9 of the Overview and in Section 4.3.1, page 35, of the Task Force Recommendations, the Task Force recommends that "CDRH should also encourage Industry and other constituencies to submit proposed guidance documents, which could help Center staff develop agency guidance more quickly."

Adoption of this proposal will be beneficial in the more efficient creation of guidance documents and will foster a more cooperative partnership between CDRH and the device industry.

**9. Task Force recommendations regarding Notice to Industry letters regarding changed regulatory expectations**

On page 9 of the Overview and in Section 4.3.1, page 35-36, of the Task Force Recommendations, the Task Force recommends that "CDRH establish as a standard practice sending open "Notice to Industry" letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations on the basis of new scientific information."

Streamlined notification of changes in regulatory expectations will be beneficial. However, as noted above, Industry input should be sought at the formative stages in evaluating the "new scientific information."

**10. Task Force recommendations regarding online labeling repository**

On page 10 of the Overview and in Section 4.3.1, page 36, of the Task Force Recommendations, the Task Force recommends that "CDRH take steps to improve medical device labeling, and to develop an online labeling repository to allow the public to easily access this information."

As with the Working Group recommendation regarding electronic submission of labels, this recommendation should have a positive impact by creating greater transparency at minimal cost.

**Covidien – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0034**

David A. Olson
*Vice President Regulatory Affairs*

COVIDIEN

October 4, 2010

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

http://www.regulations.gov

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

Dear Sir or Madam:

Covidien is submitting these comments in response to the Food and Drug Administration's (FDA, or the Agency) request for public comment on a two-volume set of documents entitled, "Center for Devices and Radiological Health Preliminary Internal Evaluations," 75 Fed. Reg. 47307-47308 (August 5, 2010).

Covidien believes the basic structure of the 510(k) process is sound, has served patients well, and helps facilitate device innovation. Although the recommendations contained in the 510(k) Working Group Report include a number of steps we believe will improve the 510(k) process, there are a number of proposed changes, if implemented, that will result in a significant disruption to the 510(k) process. These range from changes in the fundamental basis for product clearance to disclosing design schematics in a publicly available database.

Covidien is a manufacturer of a diverse range of products organized in three segments: Medical Devices, Pharmaceuticals and Medical Supplies. As a member of AdvaMed, the Advanced Medical Technology Association, we endorse the comprehensive comments AdvaMed has submitted to the docket on this topic. In addition, we are providing our own comments on key issues believed to have the greatest impact on Covidien and the medical device industry in general.

Our comments are as follows (identified as 'Response') after the applicable 'FDA Recommendation':

15 Hampshire Street
Mansfield, MA
02048

508-261-8530 [T]
508-261-6694 [F]

**FDA Recommendation:** *CDRH should clarify the meaning of "substantial equivalence" through guidance and training for reviewers, managers and industry. The Working Group recommends that CDRH revise existing guidance to consolidate the concepts of "indication for use" and "intended use" into a single term.*

**Response:** Covidien agrees with the recommendation to better train reviewers and industry on the terms "substantial equivalence" , "intended use" and "indication for use" to help reduce inconsistencies in how the terms are used. As the FDA report points out, "CDRH does not require that a new device have 'indications for use' that are identical to those of the predicate device." This implies that devices can have different indications for use than their predicate(s), but still have the same intended use for determination of substantial equivalence. Although the report recommends a continuation of this practice, combining the concepts of "indications for use" and "intended use" into a single term would likely introduce more confusion into substantial equivalence determinations. As the "intended use", for a product subject to a 510(k), must be the same as that of the predicate device to be considered "substantially equivalent", eliminating the "indications for use" section in the labeling ( by consolidating the term with intended use), will inhibit any new indicated use of products. This will effectively bring innovation and expansion of technology to a halt. The consolidation of the terms will have the effect of reducing the 510(k) program to the review and clearance of devices that are identical, not substantially equivalent, as provided in the Federal Food, Drug, and Cosmetic Act, to their predicates. Covidien is concerned that this change will result in a large number of denials of clearance for label changes related to indications for use.

Such a significant departure from a well-established practice that potentially involves a different statutory standard of analysis ("identical" versus "substantially equivalent") will significantly affect our industry as a change would involve a change of statute and of regulation.

**FDA Recommendation:** *CDRH should explore the possibility of pursuing a statutory amendment . . . that would provide the Agency with express authority to consider an off-label use, under certain limited circumstances, when determining the "intended use" of a device under 510(k) review.*

**Response:** Covidien is concerned that such a change would allow the Agency to deny a 510(k) or require companies to submit additional data in support of uses for which they do not intend the device to be used. The Food and Drug Modernization Act of 1997 enacted current statutory limitations on considerations of off-label use. The FDA's current proposal would essentially return to a standard in which FDA would evaluate an "implied" intended use based upon capabilities of a device.

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

**Response:** Covidien does not believe there is a need for stricter criteria regarding what predicate devices are eligible for use in 510(k) submissions. Under the current law, any legally marketed device, with the same intended use as the subject device, can be used as a predicate, regardless of whether it has become obsolete due to technological advances, or is no longer on the market. Many manufacturers, including Covidien, market "older" products that meet current standards of care and represent a cost effective alternative to other products and these products continue to be valid predicates. Any suggestion that certain devices should not be available to be used as predicates due to length of time on the market, for example, would be arbitrary and capricious without attendant safety issues.

If the Agency is concerned that a device is unsafe or ineffective it has the authority to bring an enforcement action and remove the device from the market. The Agency could also reclassify a device if it believed additional controls were required to assure safety and effectiveness.

Arbitrarily limiting the pool of predicate devices would have a profound effect on the industry. For example, if FDA were to require comparison to the original device for which equivalence was granted, companies would have to re-establish safety and effectiveness of previously cleared indications for each new device. This will have a detrimental effect on innovation.

Moreover, if FDA limits the number of predicate devices and also eliminates the distinction between intended use and indications for use, it will be much more difficult for a potential predicate to meet the intended use requirement. Industry will be limited to developing devices that can be compared point-by-point to a limited pool of predicates, thereby hampering the introduction of new materials, technologies and designs.

**FDA Recommendation:** *CDRH should 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". . .*

**Response:** Covidien strongly believes that the use of multiple and split predicates is an important part of the 510(k) process. Contrary to FDA's public statement (August 31, 2010 webinar) that it is not the Agency's intention to force more devices onto the PMA path, eliminating the use of split predicates would automatically place existing devices with cleared indications for use that are classified as Class II into Class III due to differences in technology.

Manufacturers develop new technology to address the same intended use for a number of reasons, including to work around intellectual property infringement issues and as a response to clinician feedback of the current technology. FDA has a long standing policy of accepting split predicates provided the indication is the same for both predicates and the subject device and the subject 510(k) includes comparative performance data to that of the predicate. As CDRH has recently required submission of the risk analysis for traditional 510(k)'s, they will have the ability to review and evaluate the potential hazards associated with any new device or technology. To disallow the use of split predicates will reduce use of the 510(k) program to devices that are identical, not substantially equivalent to their predicates.

**FDA Recommendation:** *CDRH should revise existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k).*

**Response:** As technologies have evolved, it is of course important that FDA maintain the relevance of guidance documents. In that respect, Industry welcomes such updates. If, however, the updated guidance goes beyond clarification, the application of the new guidance must be forward looking and properly implemented. Where the revised guidance would result in the new requirement to file a 510(k) for changes that were previously not addressed in the existing guidance, this must be implemented in accordance with the principles of notice and comment rulemaking.

**FDA Recommendation:** *CDRH should 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).*

**Response**: It is not clear what types of changes that FDA would expect to be included in periodic updates. The use of the term "any modification" in the proposal raises a concern that this requirement may mirror similar requirements for PMA devices and NDA drugs. Any requirement to include detail in periodic reports should be specific to those aspects that would not trigger a new 510(k) submission.

In addition, the following categories of changes would not today require a 510(k), and we believe should be specifically excluded from any requirement for periodic reporting:

- **Labeling changes** - Many products cleared by 510(k) are sold globally, and must comply with a variety of national and regional requirements for label content. As these requirements change, symbols may be added or removed, bar code formats change, international license numbers may be added or changed, and languages may be added. In addition, it is common practice to produce private label products which are identical to existing devices except for brand designation. Listing every label change

in a periodic report would overwhelm the review process, and generate needless work.

- **Changes to transport packaging** – Although information about transport packaging may be provided in a 510(k) submission, the information is not essential to the evaluation of the devices safety and effectiveness. The current system requires manufacturers to properly validate changes to transport packaging and such changes do not require FDA notification.

- **Changes to manufacturing equipment** – Replacement of capital equipment such as packaging and molding machines in a manufacturing facility occurs periodically due to the finite life of the equipment. Often, because of innovation in equipment design, the new equipment is not an exact duplicate of the previous. It is the manufacturer's responsibility to validate the new equipment and assure no change results in the products which are made by the equipment, but no additional submission should be required.

- **Changes in manufacturing location** – While a 510(k) submission may include the manufacturing location, the transfer of a product among facilities is not itself a change in design. A 510(k) clearance is not linked to a specific manufacturing location or quality system. As it is a routine practice to consolidate and transfer manufacturing locations for 510(k) cleared devices, these types of changes should not be included in any periodic reporting requirement.

While it is clear that FDA intends to phase in this requirement by device risk category, it is not clear how this would be applied with respect to changes previously implemented based on the evolution of FDA guidance regarding 510(k) submission requirements. We believe that any guidance related to device modifications should not be applied retroactively.

**FDA Recommendation**: *The 510(k) Working Group recommends that CDRH should take steps through guidance and regulation to facilitate the efficient submissions of high-quality 510(k) device information, in part by better clarifying and more effectively communicating its evidentiary expectations through the creation, via guidance, of a new "class IIb" device subset. The 510(k) Working Group recommends that CDRH develop guidance defining a subset of class II devices, called "class IIb" devices, for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting, would typically be necessary to support a substantial equivalence determination.*

**Response:** Covidien supports creation of a focused subset of Class II products for which additional guidance can be provided. However, we have concerns with the way this has been presented in the recommendation from the 510(k) Working Group, and therefore, cannot support it as written.

It has long been recognized by FDA and industry that many Class II products require additional guidance to facilitate efficient submissions. Yet, all along the resource burden to create guidance documents has inhibited the Agency from creating them. The recommendation of the 510(k) Working Group to identify a subset of products for which guidance can be created as a whole (avoiding the burden of creating individual guidance documents) is a reasonable approach to closing this identified gap in guidance. However, creation of such a guidance document must be approached in a manner to ensure that there is true benefit from the guidance and generation of the resultant evidence. We are concerned that the Agency maybe overly zealous in identifying which products should be included in the subset which will undermine the effectiveness of the guidance due to resource constraints at the Agency. This recommendation from the 510(k) Working Group is overly broad and does not provide details of the Agency's thinking in how this will actually be implemented. It is our position that in order to be successfully implemented, this subset should be a small, focused group of products.

In undertaking the development of guidance for a Class II subset we recommend that the FDA:

- Limit the scope of products within this subset to those higher risk devices where public safety will benefit and clear guidance is needed; and
- Exclude devices for which device-specific guidance already exists.

While creation of a focused Class II subset of medical devices would be a reasonable addition to the 510(k) process to ensure consistency and availability of more guidance around the higher risk Class II devices, it is imperative that we recognize that there are Class II devices associated with medium risk for which additional requirements would not be necessary. It is important to recognize that the existing 510(k) process has been a successful and effective program in clearing safe and effective devices (as evidenced by reports on recalls presented at the July 2010 Institute of Medicine meeting on the 510(k) process and the recently released Battelle report). FDA should avoid imposing the lengthier and more burdensome PMA process on products of moderate risk. Through effective guidance the FDA can ensure appropriate and consistent data is submitted and reviewed to confirm safety and effectiveness, while not interfering with the proven efficiencies of the 510(k) process.

**FDA Recommendation:** *The 510(k) Working Group recommends that CDRH, as part of the "class IIb" guidance described above, provide greater clarity regarding the circumstances in which it will request clinical data in support of a 510(k), and what type and level of clinical data are adequate to support clearance. CDRH should, within this guidance or through regulation, define the term "clinical data" to foster a common understanding among review staff and submitters about types of information that may constitute "clinical data." General*

*recommendations related to the least burdensome provisions, premarket data quality, clinical study design, and CDRH's mechanisms for pre-submission interactions, including the pre-IDE and IDE processes, are discussed further in the preliminary report of the Center's Task Force on the Utilization of Science in Regulatory Decision Making (described further in Section 2, below). That report also recommends steps CDRH should take to make well-informed, consistent decisions, including steps to make better use of external experts.*

**Response:** Covidien agrees with the 510(k) Working Group recommendation that further clarity is needed regarding the circumstances under which clinical data may be required for the subset of Class II devices (as well as the types and levels of such data). Risks to public health and overall device safety should remain the guiding principles in determining what type and level of data may be required. Depending upon the relevant attributes or risks with a product, appropriate 'clinical data' may be prospective clinical trials on the product performed under an Investigational Device Exemption granted by the FDA, but also may be clinical data from foreign experience or studies, published peer reviewed studies, retrospective clinical studies, preclinical studies, or similar type data. Covidien recommends that FDA establish a broad definition of 'clinical data'. FDA typically discusses such requirements with manufacturers during Pre-IDE meetings and, therefore, has the mechanism to specify the type and level of data appropriate for the device. For purposes of consistency across applications, reference to the clinical data type and level should be in the 510(k) Summary for a device and hence would be available with the predicate device documentation.

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

**Response:** Covidien questions the need for greater use of FDA's postmarket authorities and the need to seek greater authority to require postmarket surveillance studies as a condition of clearance for certain devices. We believe that the need to generate additional safety and effectiveness data in the postmarket setting goes against the basic premise of the 510(k) regulatory process. If a device is recognized as 'substantially equivalent' to a predicate device as the basis of the FDA's clearance of a device, this means it is substantially equivalent in safety and effectiveness to a device already cleared by FDA, or to a pre-amendment device. If this is the case there should be no reason to engage in further postmarket surveillance studies. To evaluate the continued safe and effective use of cleared devices FDA already has the mechanisms to monitor the status of devices through the Medical Device Reporting (MDR) program.

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

**Response:** In the FDA guidance document entitled, "Frequently Asked Questions on the New 510(k) Paradigm" (October 22, 1998), the Agency openly acknowledges that all verification and validation activities are typically not complete at the time of submission. While those activities identified by the risk analysis are required at the time of submission (in the case of a Special 510(k)), the remainder are "not usually performed until just prior to marketing." Therefore, the manufacturing information required for any Class II device should be limited to general descriptions that satisfy the Agency's concerns without providing the details of specific processes that may not be validated at the time of submission. Covidien recommends that the requirement for manufacturing information be limited to devices where manufacturing processes are truly viewed as potential concerns affecting public health.

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

**Response:** The 510(k) process functions through demonstration that a medical device is substantially equivalent to a predicate device, not on manufacturing capabilities. FDA has extensive regulatory and enforcement tools at its disposal to evaluate a manufacturer's capabilities to comply with current Good Manufacturing Practices (cGMP) and for prohibiting the distribution of devices in the event that a significant failure is identified that could present a serious risk to human health. FDA evaluates cGMP compliance during regular inspections of registered manufacturers and has numerous tools available, such as issuance of FDA Form 483 Inspectional Observations, warning letters, product recall mandates, product sampling, product seizures, injunctions, import detention, etc., as mechanisms for protecting public health where violations have been identified. Judgment of substantial equivalence should not be tied to cGMP compliance. These are processes that operate independently. As such, the need for pre-clearance inspections for Class II products ventures beyond the demonstration of substantial equivalence. Moreover, pre-clearance inspection would require a statutory change.

**Conclusion:**

In Covidien's view, many of the proposed changes to the 510(k) process, if implemented, will result in an increased burden on manufacturers, and CDRH reviewers, and effectively eviscerate the 510(k) program. In contrast to the stated goals of the 510(k) Working Group's recommendations as provided in Dr. Shuren's message accompanying the proposals these recommendations will not foster medical device innovation or enhance regulatory predictability. If anything, these recommendations may add new scientific requirements, new regulatory hurdles, and additional uncertainty to a regulatory process that is already non-transparent and unpredictable.

In light of the lack of data to support the need to overhaul the 510(k) process, we urge the Agency to avoid adding non-value-added burdens in response to pressure from those unfamiliar with the current process. We appreciate the opportunity to provide comments on this important topic.

Respectfully submitted,

Covidien

By: 

David A. Olson
Vice President, Regulatory Affairs

**Zimmer, Inc. – Comment (posted 10/14/10)**

Dear Sir or Madam, Please find attached comments from Zimmer, Inc. regarding Docket FDA-2010-N-0348. Regards, Carol Vierling

No comments attached

**FDA-2010-N-0348-0035**

**Underwriters Laboratories – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0036**

**Response of Underwriters Laboratories, Inc. (UL)**
**Food and Drug Administration Federal Register Notice (75 FR 1501)**
**Docket Number FDA-2010-N-0348**

**CDRH 510(k) Working Group Preliminary Report and Recommendations**

**October 4, 2010**

## INTRODUCTION

Underwriters Laboratories Inc. (UL) respectfully submits these comments in response to the recently published preliminary internal evaluation of the Center for Devices and Radiological Health (CDRH) 510(k) Working Group.

UL is an internationally recognized product safety testing and certification organization. Founded in 1894, UL has earned a reputation as a leader in product safety standards development, testing and certification. UL evaluates 19,000 types of products, components, materials, and systems annually, with twenty billion UL marks appearing on 72,000 manufacturer's products each year –including a wide-variety of medical devices. UL's work supports governmental product safety regulations, and complements federal, state and local product safety initiatives.

UL's Health Sciences business includes testing and certification services for medical devices, in-vitro diagnostic devices, and laboratory equipment for use in healthcare settings that are subject to regulatory approvals by FDA and other public health authorities around the world. Today, UL is the largest and most well known third party certifier to review submittals under the Food and Drug Administration's (FDA) 510(k) program. UL's engineers have reviewed more 510(k)s in the FDA third-party program than any other accredited entity. Protecting consumers and safeguarding the public is the mission of UL, ultimately driving our Health Sciences business to be a leading provider of end-to-end regulatory, certification, and registration services for the industry. Our breadth and experience in the medical device sector makes UL particularly well positioned to provide insight regarding the merits of the FDA's current 510(k) program, as well as the initial CDRH recommendations to modify the program. In addition to the comments found in this submission, UL wishes to be a resource for the FDA as it continues working to improve patient and user safety in the United States.

## BENEFITS OF THIRD PARTIES TO THE 510(K) PROGRAM

In general, UL believes that the current 510(k) program works well for industry, and that the ability of manufacturers to use private, third party organizations to conduct 510(k) reviews effectively streamlines the medical device approval process. The continued and expanded reliance on accredited independent third parties in the 510(k) program would be an asset to both the FDA and device manufacturers. It is imperative for an accredited, independent laboratory to safeguard its corporate integrity in order to remain in business; therefore third parties like UL take their responsibilities seriously and diligently follow program guidelines.

Further, independent third parties serve as a solution to inevitable tensions between the desires of device innovators for speed and efficiency, and the desires of users (doctors and patients), as well as the FDA for safety and effectiveness. Third parties participating in device approval programs in the United States, Europe, Canada, Japan and other markets are balancing these goals, helping review product compliance in a way that accelerates time to market beyond what the government itself can achieve, so that medical

institutions can sooner have access to the equipment they require. Since the 510(k) program's inception, thousands of devices have been reviewed by third parties prior to the FDA, and sent to market weeks earlier than if sent directly to the government agency.

We are encouraged by the FDA's preliminary report, which suggests implementing a system promoting the optimal use of third party certifiers, and providing third parties with adequate resources to make informed decisions. As mentioned in the report, the FDA found that the quality of third party reviews was highly variable; 49% of submissions that went through a third party review had to go through another level of review because of the need for additional information. The FDA has suggested the implementation of a process to efficiently determine which devices would be appropriate for third-party review, as products and technology change over time, and to also look for opportunities to provide more information to third party reviewers. UL is supportive of these improvements to the program. We also hasten to point out that third-party reviewers, like UL, have always contacted the FDA and secured this additional information on our own. Understanding that some third parties may not have taken those additional steps, the FDA's recommendation to provide information to all in advance would surely enhance the program.

UL believes that third party expertise has remained largely untapped by the FDA in its 510(k) program, and the benefits of relying on third-parties have historically been overlooked, in spite of the safeguards that currently exist in the statute. The FDA Modernization Act of 1997 authorized the FDA-accredited third parties to conduct 510(k) reviews. The original intention of the 510(k) program was to extend FDA resources by allowing third parties to assess low risk products, thus enabling the FDA to concentrate on higher risk products. In accordance with requirements in Section 523 of the Act, a number of features were included to maintain a high level of quality in 510(k) reviews managed by third parties. The US Congress provided these safeguards to ensure that no undue influence would impact the quality and safety of low-risk medical devices. We strongly recommend that the FDA consider the merits of increasing and enhancing third party involvement as it continues to review possible improvements to the 510(k) review process.

## 510(k) REFORM RECOMMENDATIONS

UL believes that the FDA's preliminary evaluation could have gone further to strengthen the role of third-parties in the 510(k) review program. **One way to do this would be to establish a stricter accreditation process for 510(k) reviewers that would involve establishing more rigorous criteria to become an approved reviewer.**

For example, the Occupational Safety & Health Administration (OSHA) safety standards require that specified equipment and materials (products) be tested and certified for safety by an OSHA-recognized organization. OSHA's Nationally Recognized Testing Laboratory (NRTL) Program fulfills this responsibility by recognizing the capabilities of private sector testing organizations to test and certify such products for manufacturers. We believe the NRTL Program, in operation since 1988, is an effective public and private partnership. Rather than performing product testing and certification itself, OSHA relies on private sector organizations to accomplish it. This helps to ensure worker safety, with existing private sector systems performing the work rather than establishing and maintaining government facilities to do this. To become recognized, an organization must meet OSHA's requirements. Initial recognition, valid for 5 years and for a specific scope of recognition, is granted if the application and an on-site review of the organization demonstrate the applicant is completely independent, has the capability (including equipment, personnel, and quality assurance), and meets other requirements to test and certify products for safety. An organization must have the necessary capabilities both as a testing laboratory and as a product certification body to receive OSHA recognition as an NRTL. UL believes the FDA could develop

an accreditation program that is similar to the one OSHA uses to maintain a high bar in terms of capability and integrity for third party 510(k) reviewers.

This rigorous program would ultimately allow the FDA to rely on the decisions of the third party reviewers in the 510(k) program, without having to send all of the related information back to the FDA for a final review and decision. Third parties in the FDA's program would be accountable to the agency for the decisions that they make in the marketplace, and would risk being removed from the program by the FDA if they did not strictly adhere to program guidelines, or if they otherwise proved incompetent or incapable of doing the reviews. Using third parties to evaluate the lower classes of devices that are most commonly used in the marketplace would allow the FDA staff to focus on the most sophisticated, innovative and essentially risky devices before they come to market. The FDA need not sacrifice vigilance or quality by including third parties in the 510(k) process. On the contrary, third parties are able to provide a fast, nimble, and closed-loop process where resources are more efficiently allocated than the government can achieve. Overseeing this accreditation process, rather than getting involved in the actual 510(k) reviews would yield time and resources back to the FDA so that it can focus on the more challenging elements of its regulatory responsibilities. **UL believes that the FDA could actually recommend the development of more rigorous third-party accreditation criteria described in this submission as a means of improving the effectiveness of 510(k) program itself, in concert with the other actions it has already identified.**

It should be clear that creating a robust third-party accreditation program would not be unique to the US government, nor to the FDA. UL is already playing a useful role as an accredited third party for several other US agencies, including the Occupational Safety & Health Administration (OSHA), the Federal Communications Commission (FCC). The US Department of Energy (DOE) and the Environmental Protection Agency (EPA) are currently changing their programs to ensure that products that achieve the Energy Star label for energy efficiency have been tested and certified by approved laboratories and certifiers. This is being done to improve the integrity and reputation of the program.

Similarly, in most of the industrialized countries and economic areas outside of the United States, third-parties are able to provide services for a substantial portion of the device approvals processes. In markets where the regulations allow for part or full evaluation by third parties, such as the EU, Japan, Brazil, and Canada, UL has obtained the necessary accreditations for medical and IVD products, making UL a true global partner for regulatory evaluation.

UL encourages the FDA to embrace the use of accredited third-party organizations to conduct 510(k) reviews, as a means of improving and streamlining the medical device approval process in the United States. In order for this to be most effective the FDA should consider the creation of a third-party program that would rely on the judgments of the third party reviewer, rather than routing documentation back to the FDA for final sign-off. Within its internal review, the FDA also suggested the implementation of a process to efficiently determine which devices would be appropriate for third party review, as products and technology change over time. We support this recommendation and further recommend that the FDA develop a process for regularly evaluating a list of device types eligible for third party review, and adding or removing devices, as appropriate, based on available information. CDRH should consider, for example, limiting eligibility to those device types for which device-specific guidance exists, or making ineligible selected device types with a history of design-related problems.

To support the Center in this endeavor, third parties could work in partnership with the FDA as useful filters to accurately identify any devices that require a more stringent PMA review. Placing some of this responsibility on accredited, third party reviewers to determine, through specific FDA guidance, would provide an added benefit to the agency, as long as the program would be tightly controlled and scrutinized through an appropriate accreditation program and oversight, and with transparent information on the

FDA's most current thinking regarding appropriate devices for the 510(k) program provided to all eligible third parties. In the event that a device submitted to a third-party actually required FDA review, the accredited third party would be responsible for bringing that information to the FDA's attention.

**BIG PICTURE FDA REFORM RECOMMENDATIONS**

With regard to third party participation in FDA programs, UL has observed a variety of programs designed with the intent to allow third parties to participate and expand FDA resources. Publicly, it appears that the FDA is supportive of third parties through the maintenance of such programs; however, in practice, it is nearly impossible to encourage their use by manufacturers because there are very few advantages designed into the programs today.

UL's experience with FDA programs involving third parties is not limited to the 510(k) medical device review program. We have faced similar challenges with the FDA's Accredited Persons Inspection Program (APIP) and the Pilot Multi-Purpose Audit Program (PMAP). UL has not progressed with respect to our accreditation in the program and ability to carry out assessments under the APIP and PMAP. We remain accredited as an organization; however, we do not have any auditors qualified by the FDA as third party inspectors. Our experience has been that the FDA is not supporting this process. Each candidate needs to participate in three training audits, and the availability of FDA staff to support the required training inspections has been limited. Additionally, because of the complex qualification requirements, it is a challenging task to match a manufacturer with an auditor/inspector having all requisite skills and qualifications.

Further, there are fundamental differences in methodology and reporting requirements between inspections carried out under the FDA's API program, as compared to ISO 13485-based programs like the Canadian Medical Device Conformity Assessment (CMDCAS) program. For example, records of internal audit and management may not be reviewed under the API program, but are critical to performing an audit to ISO 13485 or CMDCAS. The API program also contains additional requirements for reporting of assessments that are quite different in nature from audit reports developed under the ISO 13485 or CMDCAS programs.

UL regularly offers multiple programs in a single assessment, and the vast majority of our auditing staff is fully qualified to participate in multiple programs. As a matter of course, a single UL assessment may include: ISO 13485:2003; CMDCAS, Notified Body for Europe under the Medical Devices Directive (93/42/EEC) or In-Vitro Diagnostic Devices Directive (98/79/EC); Pharmaceutical Affairs Law of Japan (revised); Taiwanese Technical Cooperation Program (for European Manufacturers); and INMETRO Inspection requirements for Brazil. We can readily carry out joint assessments for all of these programs in a single assessment; however, due to the differences in methodology for the FDA program, we have been unable to effectively couple API program inspections with any of the other programs mentioned. It is our view that the fundamental differences between the FDA program and the ISO 13485-based programs prevailing in other parts of the world present difficult choices. As such, unless certain factors take shape to make the API program easier to work under, UL does not expect to see a significant increase in industry participation that would provide a business case to continue investing in training our staff to provide services under the program.

Third parties are also currently hampered by the FDA's inspection program. By allocating tasks suitable for third parties to those accredited persons, the FDA would have the resources to focus on helping industry develop innovative standards, develop guidance, and approve the most sophisticated devices. UL also understands that the US Congress has been focused on improving FDA's ability to conduct inspections of device manufacturer facilities overseas. The FDA should consider sub-contracting third party certifiers to do some of the needed inspections (e.g. for Class II devices). UL already has a global

footprint to do these inspections in short order. Today we have trained inspectors located in China, India, and other key markets where the FDA is looking to develop inspection sites, at immense costs to the US taxpayer. Subcontracting some of the inspections to third-parties like UL would thus save the US government significant time and money in its inspection work.

**Given the FDA's 27-year gap, in some cases, per the results of a 2008 Government Accountability Office (GAO) study on the matter, we suggest the FDA take the opportunity to bolster third party participation in these programs along with the 510(k) program.** Third party product evaluation, audits and inspections are as strong and reliable as the accreditation programs that support them. As long as the FDA puts in place a rigorous program to control independent third parties, it can rely on them to carry out these tasks with integrity, at a fraction of the cost and time it would take the Agency itself**.**

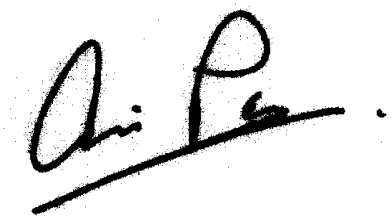
## CONCLUSION

UL applauds the FDA's conscious commitment to improving the effectiveness of the medical device approval process by conducting its own due diligence through the release of an internal evaluation. As previously mentioned, UL believes that the current 510(k) program works well for industry and that the ability of manufacturers to use private, third party organizations to conduct 510(k) reviews effectively streamlines the medical device approval process. The continued and expanded use of accredited third parties in the 510(k) program would bolster the credibility and effectiveness of the program in a time of great uncertainty. As the FDA considers ways to utilize third parties more effectively, both the APIP and the PMAP must also be taken into consideration in FDA's reform efforts. By allocating appropriate product approval, audit and inspection work to third parties, the FDA will have the resources to focus on its most pressing concerns.

UL's experience providing a range of compliance solutions for manufacturers, consumers, and government regulators globally for 116 years positions us to be a useful partner for the FDA as it navigates the challenges associated with regulating the medical device sector. The stage has been set for enhanced third party participation in FDA programs via previous calls from the US Congress to include third parties as a means of expanding FDA's resources. UL strongly believes it is time for the FDA to begin to utilize third parties more effectively, and we look forward to working with the agency in this regard.

If you have any questions or would like to discuss elements of this submission, please contact me, or Erin Grossi, UL's Director of Global Government Affairs. (Erin.Grossi@us.ul.com)

Sincerely,



Anil N. Patel,
General Manager, UL Medical

**sanofi-aventis – Comment (posted 10/14/10)**

Please take these comments into consideration. Thank you.

**FDA-2010-N-0348-0037**

sanofi aventis
Because health matters

September 14, 2010

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

**Re: Docket No. FDA-2010-N-0348**

Dear Sir/Madam:

Sanofi-aventis U.S. Inc, a member of the sanofi-aventis Group, appreciates the opportunity to comment on the recommendations contained in the above-referenced document entitled "Center for Devices and Radiological Health Preliminary Internal Evaluations."

## GENERAL COMMENTS

Sanofi-aventis welcomes this FDA initiative and the proposal for important reforms that will improve the process for medical device development, review and approval/clearance.

Sanofi-aventis believes that it is important for CRDH to have a greater level of review and oversight of drug delivery systems, as well as drug-device combinations (e.g., insulin delivery systems).

Sanofi-aventis agrees that it is important for CDRH to have a procedure for evaluating new scientific information regarding medical device technology and determining whether it requires submission of new data or the conduct of other studies. This procedure is important no matter whether the device is a stand-alone device or one used in conjunction with a specific drug. For example, new injection techniques that change the dynamics of dosing and metabolism of the drug should be assessed and a determination made as to whether specific data to confirm the effect should be required.

Sanofi-aventis agrees that CDRH should develop and seek input from outside experts on novel medical device technologies, especially as it relates to drug-device interactions.

Sanofi-aventis agrees that it is important for CDRH establish a process for responding to new scientific information about a device or device technology and determining whether the new information warrants submission of new data or FDA review.

Sanofi-aventis agrees that it is important for CDRH to enhance expertise around the human factors aspects of medical device/drug delivery systems and to ensure that potential user error is properly considered in evaluating such systems.

sanofi-aventis U.S., Corporate Regulatory Affairs Office, 4520 East West Highway, Suite 210, Bethesda, MD 20814
Tel (301) 771-4261 - www.sanofi-aventis.us

Sanofi-aventis agrees that CDRH should develop tools to facilitate more rapid communication regarding the impact of new science on its regulatory thinking to all affected parties, including to other FDA Centers involved in the review of drug and biologic delivery systems.

## SPECIFIC COMMENTS:

**Off label Use (Volume I, page 8)**
The 510(k) Working Group recommends that CDRH explore the possibility of pursuing a statutory amendment to section 513(i)(1)(E) of the Federal Food, Drug, and Cosmetic Act (21 USC §360c(i)(1)(E)) 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.

**Comment:**
*The management and regulation of off-label use is a post-market issue and should be handled as such—off-label regulation should not be incorporated as part of the 510(k) process. Enforcement action against those device manufacturers engaging in off-label activity should be strengthened; the burden should not fall on manufacturers to conduct additional premarket studies validating an off-label use when their labeling and indications for use clearly state otherwise.*

*However, if off-label use becomes part of the 510(k) process, it should be clarified as to whether the Agency would apply this change to all devices or target specific device types based upon their known off-label usage in the market. More information is required to identify what "limited circumstances" and what "compelling evidence" this proposed change would refer to, (i.e., knowledge of how the product is marketed outside the U.S., other publicly available sources regarding intended marketing/development tactics, past history of device adverse events, word of mouth). Clear explanation and consistent application of these two parameters would be necessary to avoid potential "flagging" of devices by the Agency, where one manufacturer may be unjustly subjected to increased preclearance scrutiny due to the actions of another manufacturer of a similar device.*

**"Different Questions of Safety and Effectiveness" (Volume I, page 8)**
**Insufficient Guidance for 510(k) Staff and Industry**
The 510(k) Working Group recommends that CDRH revise existing guidance to provide clear criteria for identifying "different questions of safety and effectiveness" and to identify a core list of technological changes that generally raise such questions (e.g., a change in energy source, a different fundamental scientific technology).

**Comment:**
*Although the goal of providing such guidance is commendable, it seems difficult to implement. Given the breadth of devices currently regulated as Class II, the guidance would need to be written at a low level of detail, thereby diluting the usefulness of the content and preventing the Agency from successfully providing clear and useful guidance to industry. In order for this proposal to be of utility, the Agency could consider developing device-specific guidance documents for those device types that are most problematic.*

**Rescission Authority (Volume I, page 9)**
The 510(k) Working Group recommends that CDRH consider issuing a regulation to define the scope, grounds, and appropriate procedures, including notice and an opportunity for a hearing, for the exercise of its authority to fully or partially rescind a 510(k) clearance. As part of this process, the Center should also consider whether additional authority is needed.
**Comment:**
*The Agency needs to define what would happen to currently marketed and cleared devices that have a rescinded 510(k) as a predicate, specifically if the rescinded 510(k) device is the main predicate of the currently marketed product.*

**Use of "Split Predicates and "Multiple Predicates" (Volume I, page 9)**
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".
**Comment:**
*The proposed recommendation for CDRH to develop and provide more guidance on the appropriate use of "multiple predicates" is a good one since there has been confusion in the industry and a struggle with the Agency regarding the selection of appropriate predicate devices for a submission. It would be beneficial to have more guidance regarding what the Agency deems appropriate.*

*However, disallowing the use of "split predicates" solely because a single predicate that combines intended use and technological characteristics does not exist is problematic. Such a change in the 510(k) process could potentially result in the inappropriate classification of moderate risk devices into Class III (PMA) and/or de novo, thereby increasing the burden on both industry and the Agency and stifling product innovation. The use of split predicates should not be disallowed; instead, reviewers should evaluate the use of split predicates on a case by case basis, potentially even limiting by specific device type, to ensure that the use of split predicates is done appropriately.*

**Unreported Device Modifications (Volume I, page10)**
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 below, for example, and expanding it to a larger set of devices over time.
**Comment:**
*This suggestion would impose a burden on both the Agency and device manufacturer. Therefore, it is unclear how this proposal is consistent with the goal of fostering medical device innovation. Please clarify what the Agency would be doing with this information and what type of enforcement action may result from either the change submitted or the discovery that a device modification was not submitted to FDA. The purpose of K97-1 is to allow device manufacturers the flexibility of making minor modifications to their devices without the requirement of a notification to FDA via 510(k). Such modifications determined to not require*

*a 510(k) are typically captured in "Notes or Memos to file", which can be reviewed by the Agency upon request at any time.*

*The Agency's concern regarding a cumulative impact of Notes to File on the overall safety and effectiveness of the original device as it was cleared is valid and should be addressed. Perhaps a more strict enforcement of the requirement that manufacturers provide a detailed description of all non-submitted changes in a subsequent 510(k) may be a solution. Such enforcement can be accomplished by way of a guidance document regarding the required elements of a 510(k) submission.*

**Quality of Submissions (Volume I, page 10)**
**Lack of Clarity**
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.
**Comment:**
*Enhancing the 510(k) database would allow for a more thorough predicate device search and therefore a more appropriate selection of predicate devices. This, along with standardizing the 510(k) Summary template, should address some of the issues surrounding predicate quality in 510(k) submissions. In some devices, providing a photograph/schematic of the device may not be possible without also including proprietary information; this concern needs to be considered, as foreign manufacturers typically also use this database search in their efforts to develop products in their respective countries.*

*The request to include a sample of a device may raise some concerns regarding the release of proprietary information. With a well written and sound 510(k) submission, complete with device description, labeling, schematics, mechanical/bench testing, and in some instances even clinical information, it would seem unnecessary to also mandate that a sample be included. Furthermore, depending on the device, including a sample may not be feasible.*

**Type and Level of Evidence Needed (Volume I, page 12)**
**Clinical Information**
The 510(k) Working Group recommends that CDRH, as part of the "class IIb" guidance described above, provide greater clarity regarding the circumstances in which it will request clinical data in support of a 510(k), and what type and level of clinical data are adequate to support clearance.
**Comment:**
*This appears to be an adequate proposal to help avoid delays caused by the request for additional information (e.g., clinical, manufacturing) after a 510(k) has been submitted and is under review. Due to the heterogeneity of medical devices currently identified as "class II", and due to the increasing technological complexity of many devices, a logical progression in 510(k) process would be to allow for subsets of classification. However, the practicality of establishing a new class and guidance to account for all devices requiring additional information may be problematic. It would be difficult to compile a list of specific criteria*

*required for 510(k) submissions of class IIb products given the various types of technology and devices currently in development.*

**Incorporation of New Information into 510(k) Decision Making (Volume I, page 13)**
**Recommendation:**
CDRH should take steps to enhance its internal and public information systems and databases to provide easier access to more complete information about 510(k) devices and previous clearance decisions.
**Product Codes**
The 510(k) Working Group recommends that CDRH develop guidance and Standard Operating Procedures (SOPs) on the development and assignment of product codes, in order to standardize these processes and to better address the information management needs of the Center's staff and external constituencies.
**Comment:**
*Some devices have 3 product codes assigned to their 510(k) clearance. It is unclear as to how a determination was made to assign these codes when the original submission only listed one code. Also, the Product Classification database provides useful information regarding a device (e.g., regulation number, device class, submission type, recognized consensus standards), to gain a better understanding of how these are generated and how to search this database appropriately.*

**510(k) Databases (Volume I, page 13)**
**Limited Tools for Review Staff and Outside Parties**
The 510(k) Working Group recommends that CDRH develop a publicly available, easily searchable database that includes, for each cleared device, a verified 510(k) summary, photographs and schematics of the device, to the extent that they do not contain proprietary information, and information showing how cleared 510(k)s relate to each other and identifying the premarket submission that provided the original data or validation for a particular product type.
**Comment:**
*Such an enhanced database would help the device manufacturers select the appropriate predicate device for their submission.*

The 510(k) Working Group further recommends that CDRH develop guidance and SOPs for the development of 510(k) summaries to assure they are accurate and include all required information identified in 21 CFR 807.92. The Center should consider developing a standardized electronic template for 510(k) summaries.
**Comment:**
*This proposal would greatly enhance the searchability of the current 510(k) database and lead to a more effective predicate device search.*

**Lack of Ready Access to Final Device Labeling (Volume I, page 13)**
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.

**Comment:**
*This proposal would greatly enhance the searchability of the current 510(k) database and lead to a more effective predicate device search.*

**Limited Information on Current 510(k) Ownership (Volume I, page 14)**
The 510(k) Working Group recommends that CDRH develop guidance and regulations regarding appropriate documentation of transfers of 510(k) ownership. The Center should update its 510(k) database in a timely manner when a transfer of ownership occurs.
**Comment:**
*This proposal would greatly enhance the searchability of the current 510(k) database and lead to a more effective predicate device search.*

**Well -Informed Decision Making (Volume I, page 10)**
**Unreported Device Modifications**
The 510(k) Working Group recommends that CDRH revise existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k), and, for those modifications that do warrant a new 510(k), what modifications are eligible for a Special 510(k).
**Comment:**
*It would be good if the recommended revision of the guidance would clarify the types of modifications using examples and/or particular groups of devices, where applicable.*

**CDRH Preliminary Internal Evaluations (Volume II, page 9)**
**4.3 Promptly Communicating Current or Evolving Thinking to All Affected Parties**
**Page 35-36**
The Task Force further recommends that CDRH establish as a standard practice sending open "Notice to Industry" letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations on the basis of new scientific information.
**Comment:**
*Sanofi-aventis agrees with the recommendation to inform all manufacturers if the regulatory expectations have changed. However, the mentioned "particular" groups of devices should be defined in sufficient level of detail. Additionally, the information should be included if the class of device will change/has changed.*
*Sanofi-aventis suggests that CDRH should follow "Notice to Industry" letters with a new guidance explaining the Center's new regulatory expectations as soon as possible. To make this process more robust and reduce confusion, it would be helpful to define a timeframe (e.g., 90 days).*

Sanofi-aventis supports this initiative and appreciates the opportunity to comment on these recommendations.

Sincerely,

Brian E. Harvey, M.D., Ph.D.
Vice President
*U.S. Regulatory Policy*

**Medtronic, Inc – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0038**

Susan Alpert, Ph.D., M.D.
*Senior Vice President*
*Global Regulatory Affairs*

Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432-5604
www.medtronic.com

tel 763.505.3058
fax 763.505.2630
susan.alpert@medtronic.com

October 1, 2010

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

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

Dear Sir or Madam:

Medtronic, Inc (□Medtronic□) is the global leader in medical technology□ alleviating pain, restoring health, and extending life for people with chronic conditions around the world. Medtronic develops and manufactures a wide range of products and therapies with emphasis on providing a complete continuum of care to diagnose, prevent and monitor chronic conditions such as diabetes, cardiovascular disease and neurological disorders. Each year, Medtronic therapies help more than seven million people**.**

Medtronic is pleased to submit comments on the *Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations.*

Medtronic markets a wide range of products in the United States. Many are higher risk devices and are approved for use through the PMA process. The majority of Medtronic products, however, are cleared for use through the 510(k) process. This process has worked well for the FDA, and for Medtronic and other device manufacturers, as a vehicle to provide appropriate reviews for medium and low risk devices, to foster innovation, and to bring safe and effective devices to US patients.

Medtronic appreciates the Agency□s approach to its review of the 510(k) process. We also recognize that some changes are needed to make the process more predictable and responsive to the ever-changing technologies that come before it. The agency has been open to suggestions

from industry stakeholders on the process and has incorporated many industry suggestions in these preliminary recommendations. A primary example of that is the recognition of a small subset of higher risk devices now cleared through 510(k)□s and the need for additional regulatory oversight of those products. The agency has also been open and transparent in its review of the 510(k) process and has engaged the industry and other stakeholders in town hall meetings across the United States. Additionally, the FDA has participated in the open meetings on the 510(k) process conducted by a subcommittee of the Institutes of Medicine.

Medtronic thanks FDA for the opportunity to comment on the work of the 510(k) Working Group and the Task Force on the Utilization of Science in Regulatory Decision Making. Medtronic understands and supports the FDA□s responsibilities in protecting and promoting the public health and is supportive of changes to the 510(k) program which will keep that program a viable part of the US regulatory process.

Medtronic generally agrees with and supports the comments and recommendations submitted by AdvaMed in response to the FDA preliminary report and recommendations and has the following additional comments. The comments are organized to begin with several general comments on the FDA recommendations and then address a few specific issues regarding the proposal.

**Medtronic General Comments:**

Medtronic appreciates the work that the 510(k) Working Group and the Task Force on the Utilization of Science in Regulatory Decision Making has done in developing its preliminary recommendations and, particularly, its willingness to listen to the many stakeholders in the 510(k) process. As described in the AdvaMed comments, and further below, Medtronic supports many of the proposals set forth. For example, FDA□s recommendation to streamline the de novo review process so that the agency no longer must find a new device not substantially equivalent before the sponsor can file a de novo application will benefit the agency, the industry, and patients. Also, FDA□s consistent recommendations throughout the two preliminary reports that there be a renewed emphasis upon updating guidance and providing training for FDA staff have the full support of Medtronic.

Medtronic would add four other general comments to the overall FDA recommendations. First, although any regulatory process should be reviewed, perhaps routinely, to look for areas of improvement, the 510(k) process has proven to be an effective means of clearing safe and effective products for US patients. It is a flexible tool for bringing to market medical devices that help patients and that have good overall safety records. A recent study of 510(k) recalls by Professor Ralph Hall of the University of Minnesota, presented to the IOM subcommittee on 510(k)□s, found that only 0.22% of Class I recalls were associated with 510(k) devices and related to premarket issues. Moreover, he found a similar rate of Class I recalls for devices cleared through the 510(k) process as for those that go through the Premarket Approval process. Medtronic, therefore, would encourage the FDA to make changes to the 510(k) process where those changes would have a clear benefit, but to challenge all recommendations first to ensure that they would not be counterproductive or have unintended consequences.

Second, many of the recommendations propose changes that, if implemented, would place tremendous resource demands upon the FDA, both in staff requirements and in technology. Medtronic would suggest that these resources be carefully considered, including the funding for such increases in resources. If such increases are planned, the appropriate source for such funding would be from Congressional appropriations.

Third, just as many of the recommendations would have a tremendous impact upon the FDA, they would also have a tremendous impact upon industry. FDA has acknowledged the need for training and guidance. Medtronic would suggest that major changes be phased in rather than implemented at once. The phased-in approach, with guidance and training, would provide time for FDA reviewers and for the sponsors to develop an understanding of the new expectations and to make the appropriate changes to SOP s to implement the changes.

Finally, Medtronic acknowledges that there is some discussion of the least burdensome provision in the two preliminary reports, with more discussion in the report on Science in Regulatory Decision Making. Medtronic suggests that with changes as broad as those presented in these two preliminary reports, each proposed change needs to be examined from the perspective of least burdensome alternative. In addition, we encourage FDA to utilize notice and comment rulemaking to enable full participation by stakeholders.

**Medtronic Specific Comments:**

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

Medtronic agrees with the FDA recommendation to develop guidance to provide greater clarity about circumstances in which clinical data would be needed to support the review and clearance of a 510(k) device. Medtronic is also in agreement that the guidance should address the terms clinical data and to help industry and reviewers to understand what types of information would constitute clinical data.

Medtronic recommends that FDA state clearly in any guidance it develops that clinical data is not limited only to randomized, controlled clinical trials. The guidance should allow for inclusion of clinical literature, retrospective data reviews, meta-analyses, and other sources to support 510(k) filings, as appropriate to the particular submission. FDA s goal is clearly more

nuanced than to simply graft the PMA standard of review onto 510(k)s, and the guidance should make that clear.

Additionally, Medtronic appreciates that the Task Force on the Utilization of Science and Regulatory Decision Making recognizes the importance of the least burdensome provisions, the mechanisms for industry-FDA interactions, and the important role of external experts.

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

Medtronic believes that one of the principles of the regulatory review of devices is that the reviews must be based upon the indications for use as identified in the labeling provided by the sponsor. Congress supported this principle for 510(k) reviews in the Food and Drug Administration Modernization Act of 1997 (FDAMA). Consideration of potential unapproved uses during 510(k) reviews will, of necessity, require speculation on FDA's part, which is not an appropriate standard for premarket review. Preventing safe, effective products from coming to market due to concern that physicians might (legally) use them for purposes other than their cleared indications for use is not consistent with FDA's mission and does not benefit patients. Congress has provided the FDA with significant authority in FDAMA to mandate statements in labeling regarding the likelihood of off-label use and the dangers associated with such off-label use. This is a more appropriate, and effective, tool for addressing potential off-label use through the 510(k) review.

**FDA Recommendation Regarding Posting Certain Device-Related Information:**
*The 510(k) Working Group recommends that CDRH develop a publicly available, easily searchable database that includes, for each cleared device, a verified 510(k) summary, photographs and schematics of the device, to the extent that they do not contain proprietary information, and information showing how cleared 510(k)s relate to each other and identifying the premarket submission that provided the original data or validation for a particular product type.*

Medtronic believes that publicly available databases are important sources of information for many stakeholders and appreciates that the above recommendation acknowledges the importance of the protection of proprietary information. However, Medtronic would reiterate that confidential information provided to the FDA as part of any device review process must be safeguarded by the agency from disclosure to any other party in the US or elsewhere. The risk of losing proprietary information would be a significant deterrent to innovation and to bringing new medical devices to patients.

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

Medtronic supports the FDA's interest in postmarket surveillance studies for a small subset of higher risk Class II devices. The FDA currently has the authority to require postmarket market studies for Class II devices through the Section 522 of the FDC Act. Additionally, through special controls, the FDA can require that postmarket studies, patient registries, or other surveillance be conducted. Medtronic, then, does not believe that granting additional authority to the FDA to establish "condition of clearance" studies would improve the 510(k) process, foster innovation, or promote public health.

**FDA Recommendation on Periodic Reporting of Labeling:**
*The 510(k) Working Group recommends that CDRH revise existing regulations to clarify the statutory listing requirements for submission of labeling. CDRH should also explore the feasibility of requiring manufacturers to electronically submit final device labeling to FDA by the time of clearance or within a reasonable period of time after clearance, and also to provide regular, periodic updates to device labeling, potentially as part of annual registration and listing or through another structured electronic collection mechanism. If CDRH adopts this approach, updated labeling should be posted as promptly as feasible on the Center's public 510(k) database after such labeling has been screened by Center staff to check for consistency with the device clearance. In exploring this approach, CDRH should consider options to assure that labeling could be screened efficiently, without placing a significant additional burden on review staff. For example, to allow for more rapid review of labeling changes, the Center could consider the feasibility of requiring manufacturers to submit a clean copy and a redlined copy of final labeling and subsequent updates, highlighting any revisions made since the previous iteration. As a longer-term effort, the Center could explore greater use of software tools to facilitate rapid screening of labeling changes. The Center should consider phasing in this requirement, potentially starting with only a subset of devices, such as the "class IIb" device subset described above, or with a particular section of labeling. CDRH should also consider posting on its public 510(k) database the version of the labeling cleared with each submission as "preliminary labeling," in order to provide this information even before the Center has received and screened final labeling.*

Medtronic agrees that, with a small subset of higher risk devices, a periodic report may be advisable and required as part of a special control. Medtronic would not agree, however, that periodic reporting for all 510(k) devices would better protect the public health. Such a requirement would clearly place a tremendous burden upon sponsors and upon the agency. It is not clear that FDA would have the resources to review labeling changes from thousands of devices each year on top of its existing obligations. Medtronic believes that on a case-by-case basis, mandatory periodic reports may be appropriate, but a broad-based requirement likely will not help FDA achieve its goals.

Medtronic thanks FDA for the opportunity to comment on the work of the 510(k) Working Group and the Task Force on the Utilization of Science in Regulatory Decision Making. Medtronic looks forward to continuing to collaborate with FDA in initiatives that will foster innovation and help to bring needed medical devices to US patients.

Sincerely,

Susan Alpert, Ph.D., M.D.
Senior Vice President, Global Regulatory Affairs

**American College of Cardiology - Comment (posted 10/14/10)**

**FDA-2010-N-0348-0039**

Helping Cardiovascular Professionals
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**Heart House**
2400 N Street, NW
Washington, DC 20037-1153
USA

202.375.6000
800.253.4636
Fax: 202.375.7000
www.acc.org



October 4, 2010

The Honorable Margaret A. Hamburg, MD
Commissioner
Food and Drug Administration
5630 Fishers Lane, room 1061
Rockville, MD 20852

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

Dear Commissioner Hamburg:

The American College of Cardiology (ACC) is pleased to submit comments on Food and Drug Administration's (FDA's) proposals for revisions to the 510(k) medical device approval process. The ACC is a professional medical society and teaching institution made up of 39,000 cardiovascular professionals from around the world – including 90 percent of practicing cardiologists in the United States and a growing number of registered nurses, clinical nurse specialists, nurse practitioners, physician assistants and clinical pharmacists. We appreciate the opportunity to provide input on the availability of information furnished to the public.

On a daily basis, cardiovascular professionals rely on medical devices and pharmaceuticals approved by the FDA to furnish high quality care to patients. The ACC is a strong supporter of innovations in care and treatments for cardiovascular conditions. At the same time, the ACC understands the mission of the FDA requires the government to strike a balance between protecting the public health and encouraging creativity and scientific advancement. The College urges the FDA to move carefully in this arena and engage in extensive consultation with industry before making any changes to the device approval process.

The ACC also encourages the FDA to ensure that the medical device approval process is clear and predictable and that the path for navigating it is publicly available and easily understood. This will allow medical device manufacturers to understand their objectives in the early stages of product development. It will also prevent delays in the approval process that create additional work for both the FDA and industry when requirements are misunderstood, causing the submission of incomplete applications. Ultimately, unnecessary resource usage is minimized when all parties understand initially what is expected of them, benefiting all concerned.

Additionally, the ACC urges the FDA to follow the rules of good governance while considering changes to the 510(k) process. Transparency is critical to this process, and publicizing these reports is an important demonstration of the FDA's commitment to open government. The College also believes that formal rulemaking

processes should be used. This will allow interested individuals and organizations to comment and require the government to respond to those comments in writing publicly, as provided under the Administrative Procedures Act.

The College has a strong commitment to evidence-based medicine, and this applies to approvals for medical devices, as well. Science must be the foundation of all approved medical devices. Any changes to the 510(k) medical device approval process must not stray from this fundamental principle. Medical devices unsupported by scientific evidence should not be approved, and the approval process must protect against that. The ACC urges the FDA to ensure that any changes to the approval process are supported by science and that any decisions made through the approval process will also be required to be supported by science.

Overall, the ACC supports efforts by the FDA to find the appropriate balance between fostering innovation and ingenuity and protecting the public health. We look forward to working with the FDA on this and other related issues. Please direct any questions or concerns to Lisa P. Goldstein at (202) 375-6527 or lgoldstein@acc.org.

Sincerely,

Ralph G. Brindis, M.D., M.P.H., F.A.C.C.
President

cc: Jack Lewin, MD – CEO, ACC

**Madeleine Baudoin – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0040**

To Whom It May Concern: BIOCOM leads the advocacy efforts of the Southern California life science community with more than 550 dues paying members including biotechnology, medical device, and biofuel companies, universities and research institutions, as well as service providers. In our mission of providing feedback and communication between the industry and regulators, we are writing in response to the FDA?s CDRH Internal 510(k) Working Group Report, 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 for Comment." The proposed recommendations in the report include many changes to the 510(k) process that could impact the development and clearance of medical devices. There are areas where BIOCOM feels there is good alignment with the industry; for example, BIOCOM agrees with the approach CDRH's working group recommends for reforming the ?De Novo? process. This includes steps to encourage pre-submission engagement between submitters and review staff, recommendations related to sound changes that streamline and clarify the expectations for de novo requests, what information should be submitted to determine eligibility for de novo classification, and recommendations which would establish baseline device-specific special controls. BIOCOM agrees the changes CDRH has proposed will help address inefficiencies and improve predictability. Although the spirit of many of the proposed recommendations included in the CDRH Internal 510(k) Working Group Report appear to attempt to address what steps CDRH might take to improve the 510(k) program, a concern equally shared by the industry, BIOCOM has strong objections and concerns related to the following recommended changes: "Off-Label Use" BIOCOM has strong objection to the working group?s recommendation which sugges

**BIOCOM – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0041**

BIOCOM

September 28, 2010

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

**RE: BIOCOM Response to the "Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations; Availability for Comment." [Docket No. FDA-2010-N-0348]**

To Whom It May Concern:

BIOCOM leads the advocacy efforts of the Southern California life science community with more than 550 dues paying members including biotechnology, medical device, and biofuel companies, universities and research institutions, as well as service providers. In our mission of providing feedback and communication between the industry and regulators, we are writing in response to the FDA's CDRH Internal 510(k) Working Group Report, 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 for Comment."

The proposed recommendations in the report include many changes to the 510(k) process that could impact the development and clearance of medical devices. There are areas where BIOCOM feels there is good alignment with the industry; for example, BIOCOM agrees with the approach CDRH's working group recommends for reforming the "De Novo" process. This includes steps to encourage pre-submission engagement between submitters and review staff, recommendations related to sound changes that streamline and clarify the expectations for de novo requests, what information should be submitted to determine eligibility for de novo classification, and recommendations which would establish baseline device-specific special controls. BIOCOM agrees the changes CDRH has proposed will help address inefficiencies and improve predictability.

Although the spirit of many of the proposed recommendations included in the CDRH Internal 510(k) Working Group Report appear to attempt to address what steps CDRH might take to improve the 510(k) program, a concern equally shared by the industry, BIOCOM has strong objections and concerns related to the following recommended changes:

**"Off-Label Use"**

BIOCOM has strong objection to the working group's recommendation which suggests the FDA seek authority to consider an off-label use when determining the intended use of the device under review throughout the 510(k) process. This recommendation requires statutory change, which is outside of the FDA's purview. Further, the report cites tools the FDA already has at its disposal to limit off-label usage. The recommendation is focused on off label marketing, for which the FDA already has remedies that can be deployed if desired.

BIOCOM understands that in some cases, "true" intended use could raise issues to safety and effectiveness, however giving the FDA express authority to consider an off-label use would likely put a huge burden on the manufacturer, who would be required to provide safety and effectiveness data for uses which they do not intend their device to be used. BIOCOM recommends the FDA require manufacturers to identify potential uses that may occur outside of product labeling once a device has cleared and issue warnings if needed. Clear guidance related to the manufacturer's responsibility and liability in this area should be established.

**Redefining and Clarifying "Substantial Equivalence"**

BIOCOM agrees that insufficient clarity between different technological characteristics and different questions of safety and effectiveness has lead to confusion and delays in CDRH's review and decision making process. However, CDRH's recommendation to combine "indications for use" and "intended use" into a single term under 510(k) "substantial equivalence" is not sufficient and may lead to further confusion and add to delays. BIOCOM urges the FDA to develop guidance related to how the FDA defines "intended use" and whether the Agency requires a new device to have the identical intended use as one or more predicate devices to be substantially equivalent.

**"Disallow Split Predicates"**

BIOCOM objects to CDRH's recommendation to narrow the use of multiple predicates and explore explicitly disallowing the use of split predicates would likely have a negative impact on the development and innovative devices that are developed to enhance patient care. The use of combining proven solutions, multiple predicates and split predicates, has historically aided in innovative progress. BIOCOM believes it is appropriate for the FDA to develop guidance to identify situations in which a device should be disqualified as a predicate due to safety and efficacy concerns. Guidance should clarify circumstances under which CDRH would exercise their authority to remove a device from the market or preclude its use as a predicate.

**"Rescission Authority"**

BIOCOM strongly supports the FDA's responsibility in protecting the public through its regulation of medical devices. However, the Agency already has the authority to remove

unsafe devices from the marketplace through the Food and Drug Cosmetics Act. Rescission authority over 510(k) clearance gives the FDA overly broad power. CDRH's recommendation lacks legal protections that could be put in place for medical device companies whose products would face rescission. The public could be faced with the unintended consequences of having whole categories of safe and beneficial products removed temporarily from the marketplace, and manufacturers could be faced with the undue economic burden of having their already cleared devices forced off the market. More information is needed.

**"New Class IIb"**

The addition of a new class IIb device could add an unnecessary layer of confusion for manufacturers, companies and reviewers. As the FDA already may request clinical data, it does not appear the creation of a special category is warranted. If enacted, this recommendation needs more clarification. Would class II products currently on the market be grandfathered? Would the FDA have the authority to rescind clearance on a device already on the market? How is class IIb different from class III? A significant amount of additional information is needed.

**"Requiring 510(k) Submitters to Provide all Scientific Information"**

Development of medical devices differs significantly from that of drugs, and requiring submissions to include all scientific information known or that should be reasonably known to the submitter regarding the safety and/or effectiveness of the device under review would force manufacturers to over report non-relevant information, which could significantly increase the cost and time for manufacturers to prepare 510(k) submissions without contributing to the safety or effectiveness of the devices. This recommendation could subject a manufacturer to penalties if the FDA concludes that the information provided was incomplete or inaccurate. CDRH's report fails to describe how safety and effectiveness information would be used in determining if a device is substantially equivalent to its predicate. It fails to address what information is relevant and would force the industry to over-report scientific information or risk legal breach and could lead to an increase in the need for FDA involvement in trivial invalid investigations, resulting in a costly and unnecessary burden on FDA resources.

**"Improvements to online 510(k) Database"**

BIOCOM has significant concerns over CDRH's proposal to post publicly schematics and FDA review decisions on an online 510(k) database. Design schematics and photographs should not be readily accessible to external parties unless proprietary information and intellectual property (IP) can be sufficiently protected. Searchable FDA decisions online will make it easier for companies to obtain information about their competitors, potentially leading to infringement of intellectual property rights.

**"Developing a web-based Network"**

BIOCOM has strong concerns related to CDRH's recommendation to utilize outside experts using social media technology to assist staff in understanding technologies. CDRH should enhance its support for training and professional development for review staff, but utilizing outside experts through social media could lead to confidentiality issues, conflict of interest, FACA issues and subject manufacturers to accusations related to marketing inappropriately or promotion of off-label uses. More information is needed and BIOCOM believes any experts leveraged to assist FDA staff should be from a broad range of industry, academia and VC backgrounds, and should be fully transparent in their roles.

BIOCOM respectfully requests your careful consideration of our concerns listed above. Many of the proposed recommendations would force the industry to over-report, risk legal breach and may lead a costly and unnecessary burden on FDA and industry resources. BIOCOM appreciates the work effort the FDA, the Center, and the working group have expended to generate this report. We are confident the Agency will continue working with all stakeholders in an open manner. Thank you for your consideration.

Sincerely,

Joe Panetta
President & CEO
BIOCOM

**Becton, Dickinson and Company (BD) – Comment (posted 10/14/10)**

Comments submitted to docket on behalf of BD (Becton, Dickinson and Company).

**FDA-2010-N-0348-0042**

October 4, 2010

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

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

Dear Sir/Madam:

On behalf of Becton, Dickinson and Company (BD), I am pleased to submit these comments on the recently published reports from the CDRH 510(k) Working Group and the Task Force on Science in Regulatory Decision Making.

BD is a leading global medical technology company that develops, manufactures and sells medical devices, diagnostic instrument systems, reagents and research tools. The Company is dedicated to improving people's health throughout the world. BD is focused on improving drug delivery, enhancing the quality and speed of diagnosing infectious diseases and cancers, and advancing research, discovery and production of new drugs and vaccines. BD's capabilities are instrumental in combating many of the world's most pressing diseases. Founded in 1897 and headquartered in Franklin Lakes, New Jersey, BD employs approximately 29,000 associates in more than 50 countries throughout the world. The Company serves healthcare institutions, life science researchers, clinical laboratories, the pharmaceutical industry and the general public.

BD is an active member of the Advanced Medical Technology Association (AdvaMed) and has participated along with other medical technology companies in developing the comments which have been provided separately on behalf of the entire AdvaMed membership. We urge FDA to very carefully consider AdvaMed's comments on this very important topic. Our general comments and specific recommendations are intended to supplement the points raised by AdvaMed.

We offer the following general comments on the reports:

We applaud FDA's detailed examination of the 510(k) process. It is clear from both reports that the internal review process was thoughtful and comprehensive, eliciting input and suggestions from review staff and other personnel reflecting a broad cross section of experience and skill levels within the Agency, and that great care was taken to report out the wide ranging input received. We also wish to recognize publication of these reports as a very useful step in the Agency's effort to improve transparency to the regulated industry.

While we agree that there are aspects of the 510(k) process that can be improved, we urge the Agency to carefully consider all available input and work closely with industry and other stakeholders regarding changes to this very important program. As pointed out in the reports, the 510(k) program represents the largest number of annual submissions of any premarket review program at FDA – approximately 4,000 per year over the past decade - with only a small number of these submissions raising concerns with the process or safety of the devices placed on the market. Any approach to change in the 510(k) program must carefully balance the goals shared by both FDA and industry to continue to provide safe and effective devices to the American public while also fostering innovation in medical technology.

The CDRH reports provide a tremendous quantity of feedback for consideration by FDA, industry, and other stakeholders, while providing an unprecedented insight into the opinions of numerous staff on all aspects of the 510(k) process. The sheer volume of input that was received, resulting in approximately 70 individual recommendations for change, warrants additional assessment and very careful consideration before implementation.

FDA made a significant investment on behalf of the US public when it commissioned the Institute of Medicine to convene an expert panel to study the 510(k) process and publish a comprehensive report on all aspects of the premarket notification process. This report is expected in early 2011, and we urge FDA to assure that the Agency's actions in the near term do not supplant or interfere with the final IOM recommendations.

We strongly recommend that after reviewing public commentary on the reports, FDA move ahead by identifying several of the most critical recommendations for improving the 510(k) process and communicate an implementation plan, taking into account the input received from manufacturers and other stakeholders. This would allow FDA and industry to work together to address the most immediate concerns without attempting a wholesale overhaul of the 510(k) process on a timeline that would likely overwhelm both parties.

This approach would also allow time for FDA to immediately devote much needed resources to training of FDA staff - an area that was consistently highlighted in the report as a concern – and which is very likely to increase understanding of product and technology characteristics and directly impact

consistency of reviews. An immediate focus on training, including outreach to manufacturers in order to increase opportunities for industry involvement in familiarizing reviewers with various product technologies, would increase understanding of review expectations for both FDA and industry.

We also recommend that FDA focus on those guidance areas identified by both industry and the working group as needing development or refinement as an immediate target for improvement for both the 510(k) process and individual device issues. Where industry and the working group differ in opinion regarding the guidance proposals in the report, FDA should engage in further discussion with industry.

We feel very strongly that a combined focus on training for FDA, industry, and other stakeholders and joint development of guidances would go a long way in addressing the most pressing issues that were raised by the working group regarding the current 510(k) process, and would also address many of the concerns which have been expressed by industry throughout the public dialogue that preceded publication of the CDRH reports. It is clear from the reports that the two areas of training and guidance represent the most critical opportunities for improvement in the 510(k) process as viewed by the 510(k) Working Group; this assessment is shared by regulated industry.

Another very important takeaway from the reports is the recognition that *in vitro* diagnostic (IVD) devices are already among the most highly regulated 510(k) devices reviewed by CDRH. Many IVD 510(k) submissions already include data from evaluation of performance using clinical specimens, often in head-to-head comparison against a gold standard methodology as specified by the Office of In Vitro Diagnostic Evaluation and Safety (OIVD). Performance characteristics for IVDs are required by the labeling regulations in 21 C.F.R. 809.10. In discussion of the reports during FDA's recent webinar, this common requirement for performance data in IVD 510(k)s was cited as a likely basis for inclusion of many or all IVDs in the so called 'Class IIb' subset of class II devices that is under consideration by FDA. We disagree with this approach and suggest that FDA identify only those specific diagnostic devices that justify inclusion in the small subset of devices, where the additional information is needed to make a substantial equivalence determination.

One subset of IVDs that we would recommend for consideration as part of the small subset of class II devices are those that fall in the emerging category of companion diagnostics. This categorization for these companion diagnostics would address Agency concerns around the need for increased premarket evaluation of these devices-including manufacturing data submission, pre-clearance inspections-along with potential need for post market studies, without the need to classify them as PMAs.

We share Dr. Shuren's goal of improving medical device oversight and bringing the best technologies to patients while continuing to ensure that the medical devices reaching the American public are safe and effective. We commend CDRH on its commitment to enhance regulatory predictability and foster medical device innovation. We look forward to working together with FDA to achieve these important goals.

**********

Comments on the specific recommendations from the internal reports are shown below:

**Volume I**
**CDRH 510(k) Working Group Preliminary Report and Recommendations**

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

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

– Lack of a Clear Distinction Between Terms

- The 510(k) Working Group recommends that CDRH revise existing guidance to consolidate the concepts of "indication for use" and "intended use" into a single term, "intended use," in order to reduce inconsistencies in their interpretation and application.

**COMMENT:**
We do not support the recommendation to consolidate the concepts of indication for use and intended use into a single term. For the vast majority of 510(k) devices the concepts of intended use and indications for use are well understood by both industry and FDA. In particular, these concepts are typically well understand for *in vitro* diagnostic premarket notifications and do not require significant modification. The intended use statement for an IVD typically includes a statement of the analyte that is measured, and for what purpose. The indications for use for an IVD typically describe the patient population for which the test is appropriate.

It also should be noted that there are some devices for which specific indications for use have not historically been provided, e.g. syringe with hypodermic needle, surgical drapes, manual surgical instruments. We urge FDA to consider, in its determinations going forward, these types of devices.

*Concerns about Predicate Quality*

- The 510(k) Working Group recommends that CDRH consider developing guidance on when a device should no longer be available for use as a predicate because of safety and/or effectiveness concerns.

**COMMENT:**
We want to emphasize that this issue is not a concern for 510(k)s reviewed by OIVD. Historically, OIVD advises the manufacturer of a specific product or technology to which the IVD device must be compared for purposes of the 510(k) submission – the so-called 'gold standard' – such as bacteriological media or culture for many infectious diseases.

*Use of "Split Predicates" and "Multiple Predicates"*

- The 510(k) Working Group recommends that CDRH develop guidance on the appropriate use of more than one predicate…

**COMMENT:**
We strongly disagree with any consideration of a blanket elimination of the use of split predicates, because this approach is appropriate in specific circumstances and is well understood by industry and CDRH, as indicated by the few instances cited in which the approach has been misapplied. As pointed out in the working group report, this approach is particularly applicable to certain IVD devices, and this option should be available for submitters of 510(k)s for multiparameter or multiplex diagnostic systems.

Bundling of 510(k) submissions is an appropriate approach in certain instances, such as when changes are made to a family of IVD instruments with no change in reagents, or when there is change in a reagent used with a family of instruments. BD supports the continued use of this approach based on prior consultation between the manufacturer and OIVD as necessary. When properly applied, bundling offers an approach for both industry and FDA to operate efficiently and effectively.

- 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. This training should clarify the distinction between multi-parameter or multiplex devices …

**COMMENT:**
See comment above. We support additional training on the question of multiple predicates, and strongly encourage interactive dialogue with industry, especially regarding IVDs and issues related to multi-parameter and multiplex diagnostic devices.

2. Well-Informed Decision Making

Recommendation: 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.

**COMMENT:**
We support efforts to improve the 510(k) process, but question how this would be achieved by creation of a broad category of class IIb devices. We strongly oppose the inclusion of all IVDs in the class IIb designation as proposed by OIVD during FDA's recent webinar. Incorporation of all IVDs in class IIb, based on typical inclusion of performance data using clinical samples in IVD 510(k)s is not warranted.

Class IIb should be restricted to the small subset of class II devices which have been shown to be the subject of clearly demonstrated safety concerns post marketing or those higher risk and less well-understood devices for which additional data would be valuable but which do not warrant PMA requirements.

*Quality of Submissions*

- Lack of Clarity

- The 510(k) Working Group recommends that CDRH consider adopting the use of an "assurance case" framework for 510(k) submissions. An "assurance case" is a formal method for demonstrating the validity of a claim by providing a convincing argument together with supporting evidence…

**COMMENT:**
Only limited background information on the assurance case approach was presented by CDRH during the public meeting on infusion pumps that was held earlier this year, and little else is available regarding CDRH's expectations for this new risk assessment tool. Based on the limited information currently available from CDRH, it appears that while this approach may be appropriate for certain complex devices or systems, its potential application to simple, well understood devices such as single use disposable syringes, for example, is highly questionable. Detailed guidance and training for both FDA and industry will be needed well in advance of implementation of this approach, and we suggest that the assurance case model of risk management be fully implemented for infusion pumps before it is considered for broader application to the very small subset of devices to which this approach will add value.

- 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 …

**COMMENT:**
While we generally support CDRH efforts to broaden availability of information about devices to review staff, and to the public, this recommendation can only be pursued to the extent that is practicable for both industry and FDA, and with

safeguards to ensure full maintenance of confidentiality of all information that the sponsor considers to be proprietary. We do not believe that detailed photographs and schematics that are not a part of product labeling should be publicly released. In addition, we would note that there are numerous devices for which photographs or schematics would not be useful; e.g. diagnostic reagents, software devices.

In regard to making devices available to FDA during the 510(k) review process, BD agrees that in many cases it is feasible to do this. In the case of large diagnostic instruments, in order to assure the greatest efficiency and proper installation, we would recommend that FDA and manufacturers cooperate to determine the best method to make this possible. As far as keeping a device available for a longer period of time so that FDA has access to it when used as a predicate in subsequent reviews, BD would note that this will not always be possible. For example, diagnostic reagents often have a limited shelf-life and would not be useful for comparison beyond the expiration date.

– Incomplete Information

*Type and Level of Evidence Needed*

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

**COMMENT:**
BD does not support creation of a broad new category of 'class IIb' devices.

AdvaMed's proposal to FDA supported the identification of a small subgroup of devices that are higher risk, not well-understood and for which safety concerns may therefore exist. In the case of IVDs, we recognize that 510(k) submissions routinely contain performance data which may come from evaluation of clinical samples. BD does not support either automatic classification of IVDs as class IIb products nor inclusion of most IVDs in the small subgroup of devices that AdvaMed proposed. This approach will not enhance the safety of IVDs, many of which are well understood and moderate to low risk products. The addition of pre-clearance submission requirements including pre-clearance inspections linked to individual 510(k)s or inclusion of manufacturing data, for example, would not add valuable information for products that have not generated specific safety concerns. Sweeping all IVDs into class IIb would add a tremendous, unnecessary burden to both FDA and industry and would only slow down the development of much needed diagnostics, which can help to reduce healthcare costs through early and appropriate intervention.

Additional pre-clearance data requirements should be restricted to the small subset of class II devices which have been associated with clearly identified post

market safety issues or those that warrant additional pre-clearance requirements based on level of risk and novelty of technology.

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

**COMMENT:**
See comment above. Because BD does not support the recommendation to develop a broad category of class IIb devices, and especially does not support the automatic inclusion of all IVDs in this class IIb, training on this issue would be unnecessary.

– Clinical Information

- The 510(k) Working Group recommends that CDRH, as part of the "class IIb" guidance described above, provide greater clarity regarding the circumstances in which it will request clinical data in support of a 510(k)…

**COMMENT:**
BD strongly support efforts by CDRH to provide greater clarity regarding the circumstances in which it will request clinical data in support of a 510(k), and what type and level of clinical data are adequate to support clearance- but again – only in those limited circumstances in which specific devices or categories of devices have been shown to require submission of additional data before clearance, on the basis of demonstrated safety concerns or other considerations.

– Postmarket Information

- The 510(k) Working Group further recommends that CDRH continue its ongoing effort to implement a unique device identification (UDI) system …

**COMMENT:**
BD supports implementation of UDIs in as an important component in tracking medical devices and encourages FDA to continue efforts to finalize this technology in consultation with industry and in concert with global efforts to harmonize UDI requirements. FDA should continue to very carefully evaluate the obvious differences across the full range of marketed products as it moves to implement UDIs. For example, the implications for product safety and practical implementation are very different for syringes or IVD reagents as compared to implantable devices.

– Manufacturing Process Information

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

**COMMENT:**
BD supports this approach only for the small subset of 510(k) products for which information on the manufacturing process is directly relevant to a determination of substantial equivalence. As an example, FDA may need information on an aseptic filling process; e.g. for a heparin flush syringe, to assure that the finished product will be safe for use. At the same time, manufacturing information on a diagnostic instrument will not provide any insight into the safety or effectiveness of a finished product.

*Incorporation of New Information into 510(k) Decision Making*
*510(k) Databases*

- Limited Tools for Review Staff and Outside Parties

- The 510(k) Working Group recommends that CDRH develop a publicly available, easily searchable database that includes, for each cleared device, a verified 510(k) summary…

**COMMENT:**
We encourage further development and increased usage of decision summaries such as those already provided by CDRH/OIVD for IVD devices as a valuable source of information for industry and other stakeholders.

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

1. Enhancing CDRH's Scientific Knowledge Base

Quality of Clinical Data

- The Task Force recommends that CDRH continue its ongoing efforts to improve the quality of the design and performance of clinical trials used to support premarket approval applications (PMAs), CDRH should consider expanding its ongoing efforts related to clinical trials that support PMAs, to include clinical trials that support 510(k)s.

**COMMENT:**
BD supports efforts by CDRH to improve understanding and communication of clinical trial requirements across a wide range of medical devices and diagnostics, and agree that a consistent approach to clinical trials that require such data will be very valuable.

It is important for CDRH to carefully consider those limited situations in which clinical data is appropriate for 510(k) devices, and to clearly distinguish the differences between Class III devices undergoing PMA review and those lower risk devices entering the market by the 510(k) pathway. Clinical data should be required only for those 510(k) devices which have been shown to raise questions of safety or performance that can only be addressed through such studies. The majority of 510(k) devices, especially IVD products, should not require clinical data of the type required for PMA devices. We further recommend that OIVD assess the reduction or elimination of clinical data requirements for low risk IVDs as part of the proposed evaluation. In many instances, performance data generated other than by clinical trials (e.g. side-by-side laboratory comparisons on known samples) could be supplied to meet the labeling requirements for IVDs.

- The Task Force recommends that CDRH work to better characterize the root causes of existing challenges and trends in IDE decision making, including evaluating the quality of its pre-submission interactions with industry…

**COMMENT:**
The IDE process, especially pre-IDE interactions, is a very important and valuable part of the interactive review mechanism. BD supports efforts by CDRH to evaluate and strengthen the process and improve understanding of it by both FDA staff and industry. However, we caution against any changes that would undermine the informal nature of these very valuable interactions or impede their frequency and timeliness.

**********

BD appreciates this opportunity to comment on FDA's internal evaluation of the 510(k) process. We applaud FDA's review of the 510(k) process and support the Agency's efforts to improve this very important program, which continues to be used by companies and FDA to assure that thousands of safe and effective devices and diagnostics reach the U.S. market in a timely fashion.

Sincerely,

*[Steven B. Binion for]*
Patricia B. Shrader
SVP, Regulatory & External Affairs
BD

**Johnson and Johnson – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0043**

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

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

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

Dear Sir/Madam:

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

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

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

***General Comments*:**

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

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

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

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

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

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

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

## *Specific Comments:*

### *1. CDRH Recommendation: Definition of Substantial Equivalence*

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

**Johnson & Johnson Comment**

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

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

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

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

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

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

**Johnson & Johnson Comment**

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

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

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

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

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

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

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

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

**Johnson & Johnson Comment**

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

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

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

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

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

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

## 4. CDRH Recommendation: *de novo* Classification

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

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

### Johnson & Johnson Comment

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

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

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

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

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

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

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

## 5. CDRH Recommendation: Type and Level of Evidence Needed

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

**Johnson & Johnson Comment**

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

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

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

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

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

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

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

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

**6. <u>CDRH Recommendation: Incomplete Information – Submission of All Scientific Information</u>**

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

**Johnson & Johnson Comment**

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

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

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

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

**7. CDRH Recommendation: Periodic Reporting Requirements – Labeling**

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

**Johnson & Johnson Comment**

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

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

### *Additional Specific Comments:*

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

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

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

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

## Summary of Johnson & Johnson Positions on the Working Group Recommendations

**Recommendations Johnson & Johnson Supports**

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

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

**Recommendations Johnson & Johnson Supports with Modifications**

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

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

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

**Recommendations Johnson &Johnson Does not Support**

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

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

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

## Summary of Johnson & Johnson positions on the Task Force Recommendations

**Recommendations Johnson & Johnson Supports**

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

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

**Recommendations Johnson & Johnson Supports with Modifications**

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

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

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

***Summary and Conclusion***

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

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

Sincerely,

Harlan Weisman, M.D.

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

**Thomas Bonner – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0044**

Unreported device modifications This process would be considerably cumbersome for most device manufacturers. This process would require almost all device modifications, whether materials or specification changes to be submitted to the FDA along with substantiated data for the change. Since changes in the past for cleared devices happen rather rapidly for changes that are deemed insignificant or minor, and are substantiated via a ?letter to file? the modification of the process would prohibit rapid change to a device as the industry has grown accustomed. This modification could dramatically affect a firm?s ability to supply customers with products as quickly as they expect, depending upon how promptly FDA reacts to the proposed changes once submitted. Currently a firm is relegated with the responsibility to know when a change to a device would require a new submission and this should remain with the firm?s best judgment for their devices.

**FDA-2010-N-0348-0046**

Transfer of Ownership of 510k?s FDA should update its database to include the transfer of ownership of acquired 510k?s due to a number of issues that arise frequently with device manufacturers and their customers. This issue has been on-going with FDA, and poses problems for customers investigating a company and its 510k status. Additionally, issues arise when importing devices, preventing FDA from identifying the current owner of the 510k via an electronic database. The lack of such a database causes delays and/or detention at the border, and places the burden on the manufacturers to constantly supply information to the FDA regarding 510k?s and Listings.

**California Healthcare Institute (CHI) - Comment (posted 10/14/10)**

**FDA-2010-N-0348-0045**

October 4, 2010

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

Docket No. FDA-2010-N-0348

## I. INTRODUCTION

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

### A. Description of CHI

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

### B. Why CHI has a Unique Perspective

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

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

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

## C. Importance of 510(k) to CHI Members

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

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

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

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

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

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

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

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

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

## II. PROCESS ISSUES

### A. The Reform Process Must be Thoughtful and Specific

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## B. The FDA Should Not Create a New Class IIb

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

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

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

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

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

## D. The De Novo Process Should be Logical and Efficient

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

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

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

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

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

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

## G. FDA Already Has Access to Post Market Information

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

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

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

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

## I. CDRH Reviewers and Managers Should Have Enhanced Training

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

## J. Additional Issues that FDA Should Consider

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

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

## IV. CONCLUSION

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

Todd E Gillenwater
Vice President, Public Policy

**American Medical Systems (AMS) – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0047**

AMS
Solutions for Life

American Medical Systems
10700 Bren Road West
Minnetonka, MN 55343

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

October 4, 2010

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

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

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

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

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

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

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

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

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

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

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

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

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

## II. Submitting Detailed Photographs or Schematics

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

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

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

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

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

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

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

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

## IV. Creation of Class IIb Device Subset

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

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

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

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

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

## V. Strengthening the *de novo* Process

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

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

## VI. Implementing a Uniquie Device Identifier (UDI)

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

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

## VII. Additional Rescission Authority

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

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

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

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

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

Sincerely,

Ginger Glaser
Senior Director, Global Quality
American Medical Systems

**AdvaMed State Medical Technology Alliance – Comment (posted 10/14/10)**

See attached

**FDA-2010-N-0348-0048**

October 4, 2010

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

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

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

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

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

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

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

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

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

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

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

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

Thank you for considering these comments.

Sincerely,

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

**Medical Device Manufacturers Association (MDMA) – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0049**

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

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



October 4, 2010

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

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

Dear Sir or Madam:

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

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

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

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

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

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

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

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

[3] CDRH Webinar, August 31, 2010.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[9] 21 C.F.R. §860.7.

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

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

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

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

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

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

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

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

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

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

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

Respectfully Submitted,

Mark B. Leahey
President " CEO
Medical Device Manufacturing Association

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

**Society for Women's Health Research (SWHR) – Comment (posted 10/14/10)**

Attached is a formal comment from Phyllis Greenberger, President and CEO of the Society for Women's Health Research regarding Docket No. FDA?2010?N?0348. Thank you for your consideration of this comment.

**FDA-2010-N-0348-0050**

October 4, 2010

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

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

To Whom It May Concern:

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

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

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

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

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

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

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

Sincerely,

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

**National Association for Continence (NAFC) – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0051**


62 Columbus Street, Charleston, South Carolina 29403

October 4, 2010

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

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

Dear Dr. Hamburg:

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

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

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

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

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

Sincerely,

Nancy Muller
Executive Director

**CONNECT – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0052**

Comments by CONNECT Submitted to the Food and Drug Administration Related to the Request for Comments on The CDRH 510(k) Working Group and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Reports and Recommendations, Docket No. FDA-2010-N-0348 October 4, 2010 Summary: CONNECT?s mission is to propel innovative ideas and emerging technologies to the marketplace by connecting entrepreneurs with the comprehensive resources they need to sustain viability and business vibrancy. That mission could be hindered in the medical device field if the Food and Drug Administration does not exercise regulatory caution and restraint as it seeks to reform the 510(k) review process. The legal, policy and practical uncertainties that are inevitable if restraint is not exercised could possibly dampen innovation in the field. On the other hand, if caution is exercised with an eye to the needs of innovation, especially start-up innovation and emerging technologies, the process could be enhanced in a way that further promotes and protects public health. In the absence of a clear and readily identifiable public health threat, CONNECT respectfully requests that the FDA continue to evaluate and analyze potential regulatory changes toward the goal of increased uniformity and act only where consensus exists that innovation will be accelerated and patient care advanced. Where the lack of consensus yields valid but contrasting arguments, the FDA should seek further input and use its ability to convene disparate voices toward an outcome that will clearly advance innovation and patient care.

**Comments by CONNECT**

**Submitted to the Food and Drug Administration**

**Related to the Request for Comments on**

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

**Docket No. FDA-2010-N-0348**

**October 4, 2010**

**Summary:**

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

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

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

**Introduction:**

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

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

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

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

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

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

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

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

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

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

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

**Conclusion:**

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

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

Respectfully submitted,

CONNECT, by:

Timothy Tardibono

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

**SonoSite, Inc – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0053**

SonoSite

October 4, 2010

***BY ELECTRONIC DELIVERY***

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

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

Dear Dr. Shuren:

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

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

**We ask FDA to consider the following comments and recommendations:**

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

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

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

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

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

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

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

## ***Background***

**Implementation of Report Recommendations Must Include Additional Opportunities for Public Comment**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Conclusion**

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

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

Sincerely,

Mary K. Moore
Vice President, Regulatory Affairs

SonoSite Inc.

**Medical Imaging and Technology Alliance (MITA) – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0054**

MITA
MEDICAL IMAGING
& TECHNOLOGY ALLIANCE
A DIVISION OF NEMA

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

October 4, 2010

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

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

Dear Dr. Shuren:

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

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

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

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

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

**General Comment on Process and Scope**

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

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

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

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

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

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

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

## I. MITA Comments on Recommendations Related to Predicate Devices

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**II. MITA Comments on 510(k) Submission Content**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3) Creating defined time periods for key process steps;

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

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

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

Generic Devices

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

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

Non-Generic Devices

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

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

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

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

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

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

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

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

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

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

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

## IV. MITA Comments on Internal FDA Policies and Procedures

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## V. Additional Areas for Comment

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

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

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

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

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

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

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

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

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

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

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

## VI. Conclusion

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

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

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

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

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

Respectfully submitted,

Dave Fisher
Executive Director, MITA
Vice President, NEMA

**United Spinal Association – Comment (posted 10/14/10)**

See attached file(s)

**FDA-2010-N-0348-0055**

October 4, 2010

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

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

To Whom It May Concern:

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

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

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

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

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

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

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

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

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

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

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

Thank you for considering these comments.

Sincerely,

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

**LifeScience Alley – Comment (posted 10/14/10)**

**FDA-2010-N-0348-0056**

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

952.542.3077 PHONE
952.542.3088 FAX

www.lifesciencealley.org



LifeScience Alley™

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

http://www.regulations.gov

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

**Docket No. FDA-2010-N-0348**

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

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

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

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

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

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

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

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

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

**Recommendation**

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

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

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

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

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

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

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

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

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

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

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

**Recommendation**

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

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

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

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

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

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

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

**Recommendation**

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

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

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

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

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

**Recommendation**

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

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

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

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

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

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

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

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

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

**Recommendation**

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

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

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

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

**Recommendation**

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

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

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

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

**Recommendation**

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

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

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

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

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