

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 ("nothing 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 510(k) 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 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.

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



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,

A handwritten signature in black ink, appearing to read "Alison D. Burcar", with a long horizontal flourish extending to the right.

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 $TiCl_4$ 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, $TiCl_4$, 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.

DAVID A. OLSON
Vice President Regulatory Affairs



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':

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 device's 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



**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.

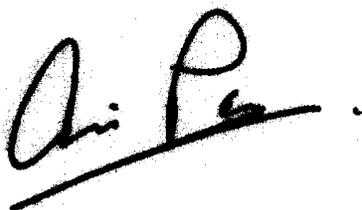
CONCLUSION

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,

A handwritten signature in black ink, appearing to read "Anil N. Patel", with a horizontal line underneath the name.

Anil N. Patel,
General Manager, UL Medical



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 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.

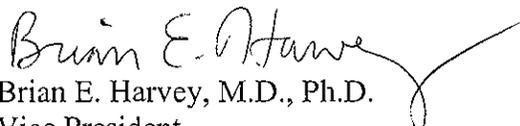
Comment:

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**

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

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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) 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), 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 SOPs 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 FDCA 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,

A handwritten signature in black ink that reads "Susan Alpert". The signature is written in a cursive style with a large initial 'S' and a long, sweeping underline.

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



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**ex officio*

Chief Executive Officer

John C. Lewin, M.D.

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

The mission of the American College of Cardiology is to advocate for quality cardiovascular care — through education, research promotion, development and application of standards and guidelines — and to influence health care policy.

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,

A handwritten signature in blue ink that reads "Ralph Brindis". The signature is fluid and cursive, with the first name "Ralph" and last name "Brindis" clearly legible.

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

cc: Jack Lewin, MD – CEO, ACC



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 led 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,

A handwritten signature in black ink, appearing to read "Joe D. Panetta". The signature is fluid and cursive, with a large initial "J" and "P".

Joe Panetta
President & CEO
BIOCOM

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 understood 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