The FDA Internal Committees' Recommendations	The FDA Internal Committees' Stated Rationales for Their Recommendations	King & Spalding's Views on Potential Impact of the Recommendations, if Implemented	King & Spalding's Comments on the Recommendations
• Enhance employee training and professional development.	This is a goal, supported by data, already identified under FY 2010 Strategic Priorities to enhance recruitment, retention, and development of high-quality employees.	Improvement in employee training and professional development may enhance the review process and lead to better retention of experienced reviewers.	
• **Improve mechanisms for leveraging external scientific expertise.**	It is difficult for CDRH to tap meaningful external scientific expertise in a timely manner.		
• Develop a web-based network of external experts.	There a need for CDRH to access information about novel technologies, new scientific issues, and improve internal scientific capabilities. The intent is to increase the use of outside experts via web-based mechanisms distinct from the regulated process of formally accessing outside experts via the Advisory Committee and other Special Government Employee mechanisms.	The strength of this proposal is that increased access to outside experts has the potential to enhance the growth of scientific expertise within CDRH. However, it is possible that the use of external experts could have decisive influence on premarket and postmarket regulatory decisions affecting single products or groups of devices. The establishment and use of any external experts should be done in a manner that assures that the identity, opinion, and potential bias of the "external expert" will be transparent to the manufacturer and the public during the review process.	We urge FDA to publish its draft standard process for the establishment and utilization of the proposed web-based network of outside panels. We reserve our comments until that proposals is published.
• Develop standard processes for use of external experts.			
• Establish enduring collaborative relationships with other science-led organizations.	Mechanism for additional access to external scientific expertise.	CDRH already interacts with professional medical and scientific associations. Establishing long-term collaborations with such experts would FDA gain insight into issues that it might not otherwise have fully considered.	We support this proposal.

The FDA Internal Committees' Recommendations	The FDA Internal Committees' Stated Rationales for Their Recommendations	King & Spalding's Views on Potential Impact of the Recommendations, if Implemented	King & Spalding's Comments on the Recommendations
Applying a Predictable Approach to Determine the Appropriate Response to New Science			
• **Establish an approach, as predictable as practical, for determining what action is warranted in response to new scientific information that could affect regulatory decisions about devices. The conceptual framework is a four-step approach. of detection, escalation, collaborative deliberation, and action.**	Across the Center, it is not clear when new scientific information warrants action by CDRH, particularly a change in evidentiary expectations for premarket review of a product or group of products.	The conceptual four-step approach proposed by FDA would greatly improve appropriate evaluation and response to new information related to a device or group of devices. However, the implementation of such a framework and the consistency of how it is applied is of great concern. The current proposal lacks important detail and definitions, such as identification of a "signal", when it should be escalated, etc.	We support the recommended conceptual framework. However, we have serious concerns about the feasibility of implementing and utilizing such a framework in a timely and consistent manner. We encourage FDA to provide greater detail, through the development of standard procedures, guidance, etc., on the implementation of the proposed framework and to invite comments from industry and stakeholders on those processes.
• Develop and implement a process of "**Signal Escalation**" of new science signals, including detection, escalation to upper management, process for deliberation, and decision for action. Also, develop metrics to determine if the new process is effective.	CDRH lacks a process that is followed by *all* review divisions to determine if new information warrants a change in evidentiary requirements for devices that are reviewed. The rationale for proposal is to ensure consistency in management of new science signals that could affect 510(k) regulatory decisions, assure open internal communication, and develop a collaborative response, as well as to, avoid duplication of effort.		CDRH is already developing a Signal Escalation process. We strongly encourage FDA to obtain stakeholder feedback on the process and to develop procedures for revising the process if the metrics show the process is not effective.
• Develop a **Collaborative Deliberation** process to determine what action, if any, is necessary in response to new scientific information. This includes establishment of a Center Science Council within CDRH, under	CDRH lacks a central authoritative team with experience and expertise - including clinical trial expertise - needed to interpret whether new requires new regulatory action.	Again, we agree with the concept of a Collaborative Deliberation process, but are concerned with the practical implementation of such a process. The development of a Center Science Council could have a profound effect on the regulation of single products or groups of devices. In addition, the Center Science Council is to serve as	We support the recommended conceptual framework. However, we have serious concerns about the feasibility of implementing and utilizing such a framework in a timely and consistent manner. We encourage FDA to provide greater detail, through the development of standard procedures, guidance, etc.,

The FDA Internal Committees' Recommendations	The FDA Internal Committees' Stated Rationales for Their Recommendations	King & Spalding's Views on Potential Impact of the Recommendations, if Implemented	King & Spalding's Comments on the Recommendations
direction of the Deputy Center Director for Science, to provide oversight and consistency in responding to new science information.		a review board to resolve certain disputes; thus, this may mitigate internal disagreements that have focused negative media and Congressional attention on CDRH. However, the use of the Center Science Counsel could lead to delays in premarket review and evaluation of new science unless FDA issues detailed procedures for its establishment and utilization.	on the implementation of the proposed framework and to invite comments from industry and stakeholders on those processes.
• Enhance data sources and methodologic capabilities for evidence synthesis and decision-making as a long-term goal.	There is a need to improve the infrastructure for quantitative science-based decision-making for device regulation because CDRH operates in environment of rapidly changing technology and science.	Improvement in data capture, methods, and analysis is a major goal for both FDA and industry regarding regulated devices. However, stakeholders have already identified concerns related to the use of real world clinical databases for low-frequency safety signal detection, including the process of determining if the signal is real, what its true magnitude is, and whether the signal is actionable (e.g., FDA's ongoing development of the Sentinnel Database).	We support this proposal and urge FDA to develop clear definitions, processes, and procedures to ensure consistency.
Promptly Communicating Current or Evolving Thinking to All Affected Parties			
• **Make use of rapid communication tools to convey changes in the Center's thinking and expectations.**	In response to new science that affects regulatory decision-making, it is difficult for the Center to communicate current or evolving thinking in a timely and meaningful manner to all stakeholders.		
• Streamline processes for developing guidance	There is need for more rapid capability to implement changes in FDA policy	More streamlined and timely delivery of needed guidance and correction of	We support this recommendation.

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The FDA Internal Committees' Recommendations	The FDA Internal Committees' Stated Rationales for Their Recommendations	King & Spalding's Views on Potential Impact of the Recommendations, if Implemented	King & Spalding's Comments on the Recommendations
documents and regulation, consistent with FY 2010 Strategic Priorities. Also, encourage industry and other parties to submit proposed guidance documents.	at the levels of guidance and rule making, particularly to address a public health concern or lessen burden on industry.	ambiguous regulations may increase predictability in the PMA and 510(k) review process. However, there must be sufficient opportunity for public comment and discussion. Additionally, the ability to actually achieve this goal may be difficult given the current limitations of CDRH staffing and resources.	
• Establish a standard practice of issuing open "**Notice to Industry**" letters to all manufacturers of a group of devices when CDRH has changed its regulatory expectations in response to new scientific data.	The Center currently lacks the ability to rapidly and consistently disseminate evolving regulatory expectations for a general type of devices. The proposed Notice to Industry letters would in effect be considered guidance and would be issued as Level 1 guidance documents. CDRH would open a public docket for submission of comments upon issuance of Notice to Industry letters and follow with more specific, detailed guidance describing the new information and changes in expectations.	The notion of clear written communication of major changes in FDA expectations has the potential to create a "level playing field" for all manufacturers when FDA changes its thinking about a group of products. However, implementation as a standard practice *prior to the opportunity for public comment and feedback from industry* may have the unintended consequence of increasing the frequency of abrupt changes in regulatory expectations for many groups of devices without appropriate input from manufacturers or the public. There is the possibility that FDA could further revise its expectations for premarket submissions for a group of devices based on comments the Agency receives after it issues the Notice to Industry letter and subsequent detailed guidance. This could create an even more "unlevel" playing field for manufacturers because some would have been required to comply with the expectations outlined in the Notice to Industry letter while others would only need to comply with the	We support the internal committee's proposal for early and frequent communication regarding new science and evolving expectations. However, we caution FDA about the potential unintended consequences of Notice to Industry letters and recommend that such letters be used to invite industry to meet with the Agency.

The FDA Internal Committees' Recommendations	The FDA Internal Committees' Stated Rationales for Their Recommendations	King & Spalding's Views on Potential Impact of the Recommendations, if Implemented	King & Spalding's Comments on the Recommendations
		revised expectations issued in the final guidance.	
• Create a web page to identify and explain the new science information that has changed the Center's regulatory expectations.	There is a need to promote better public understanding of rationale for changes in the Center's regulatory requirements across all CDRH-regulated products.	If FDA does implement the new process of issuing "Notice to Industry," an explanatory web page would provide an accurate account of FDA's thinking and provide industry with an opportunity to evaluate FDA's rationale in the context of its own specific device. The explanatory web page, however, should not identify specific devices or companies, but present information in aggregate and general format.	We support an explanatory website, if the new Notice to Industry letter process is implemented.
• Develop online access to up-to-date labeling for 510(k) devices.	"Featuring up-to-date, cleared device labeling in CDRH's public 510(k) database would allow prospective 510(k) submitters to more readily and more accurately compare their devices to potential predicates, and it would give medical professionals and device users' easy access to critical device information that would support safe and effective use."	Our views on the potential impact of the review and posting of 510(k) cleared labeling on FDA's website are discussed above in the 510(k) Report section of this table.	Our comments on the review and posting of 510(k) cleared labeling on FDA's website are discussed above in the 510(k) Report section of this table.
• **Provide additional publicly accessible information about the Center's response to new science and reasons for its actions.**	There is a lack of transparency about the rationale for particular courses of action by CDRH in response to new scientific data applicable to individual devices and groups of medical devices.		We support the higher level concept of provision of publicly accessible information about the Center's rationale for decision-making.
• Develop a publicly accessible SOP that describes the process CDRH will use to respond to new science, including "Signal Escalation" described	There is a need for clear and prompt communication in a standardized manner of new CDRH regulatory decisions and their rationale, particularly when the decision is a change in evidentiary expectations for clearance of a particular type of	It is critical that FDA define the process and criteria that it will use during "Signal Escalation," Collaborative Deliberation, and Action/Communication to publicly or not publicly communicate a change in regulatory expectations for a device	We reserve comment on the process for FDA's responding to new science until the Agency publishes the proposed SOP.

The FDA Internal Committees' Recommendations	The FDA Internal Committees' Stated Rationales for Their Recommendations	King & Spalding's Views on Potential Impact of the Recommendations, if Implemented	King & Spalding's Comments on the Recommendations
above.	product.	or group of devices. It is also critical that the process define the formal mechanisms for informing a manufacturer that "Signal Escalation" has been initiated, ensuring input of the manufacturer, and defining a process for dispute resolution.	
• Make sure all CDRH staff understand what information they are permitted to discuss with manufacturers.	Many manufacturers perceive that there is inconsistency and confusion across review teams as to what information may be communicated to the Sponsor regarding the rationale for a substantial equivalence determination. Additionally, training for CDRH staff could avoid needlessly withholding information that would clarify the basis of a particular action/decision.		We support training FDA staff regarding the type of information that can be shared, but urge the Agency to ensure that its staff fully explains the substantial equivalence determination to the submitter while ensuring that proprietary information regarding the predicate devices is not shared with other companies.
• Continue to make more premarket and postmarket information about CDRH regulated products publicly accessible thought the CDRH Transparency Website.	This recommendation is consistent with the Center's FY 2010 Strategic Priorities and the efforts of the FDA Transparency Task Force.	Continued use and improvement of the CDRH transparency website can provide industry and the public with more information about medical devices and CDRH's decision making process. However, there must be mechanisms in place to assure that confidential information will remain confidential. In addition, FDA must develop and implement policies and procedures regarding type of information the Agency will publicly disclose and timing of such disclosure.	We support this recommendation, but remind FDA that the public disclosure of information must comply with the current regulations regarding confidential, trade secret commercial information set forth in 21 C.F.R Part 20.
• Publicly release information that is currently not available, including summaries of premarket review		Posting of premarket decision summaries may increase the consistency of the review process and allow manufacturers to choose more appropriate devices as predicates or	We support this recommendation.

The FDA Internal Committees' Recommendations	The FDA Internal Committees' Stated Rationales for Their Recommendations	King & Spalding's Views on Potential Impact of the Recommendations, if Implemented	King & Spalding's Comments on the Recommendations
decisions as well as the results of agreed upon post-approval studies and required postmarket Section 522 studies.		controls in a clinical study.	

Patient, Consumer, and Public Health Coalition – Comment (posted 10/14/10)

FDA-2010-N-0348-0063

October 4, 2010

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

Comments of the Patient, Consumer, and Public Health Care Coalition

on

"Center for Devices and Radiological Health Preliminary Internal Evaluations"

[Docket No. FDA-2010-N-0348]

As members of the Patient, Consumer, and Public Health Coalition, we support most but not all of the preliminary recommendations of the 510(k) Working Group and the Task Force on the Utilization of Science in Regulatory Decision Making.

We do not support the recommendations regarding the de novo process or third party review. We also want to express our concerns about the Class IIb category and the off-label use recommendations.

We agree with the Working Group's finding that "CDRH does not currently have an adequate mechanism to regularly assess the quality, consistency and effectiveness of the 510(k) program."[1] That is consistent with what members of our Coalition have said in our March 19 public comment and at the FDA's "Strengthening the Center for Devices and Radiological Health's 510(k) Review Process" meeting in February.

The scope of this finding is broad and cuts to the heart of the problem with the 510(k) program. The 510(k) program clears devices based on similarity to predicate devices. But if a new 510(k) device is based on a predicate that had poor quality, safety issues, or was ineffective, how can we expect the new device to be any better? And if the new device is made of different materials or uses a different mechanism of action, it is impossible for the FDA (or doctors or patients) to be certain that the new product is as safe or as effective as the predicate.

Below are our comments on several of the Working Group's specific recommendations.

Substantial Equivalence

We agree with the Working Group that CDRH should clarify the meaning of substantial equivalence through guidance and training. Substantial equivalence must be consistently

interpreted by CDRH, and the interpretation should be tightened to safeguard the public health.

We also agree that the FDA should clarify what it means that the product should have the same intended use. We agree that the interpretation has been flexible to the degree that it is unpredictable. We were very concerned that the CDRH's own survey found confusion among reviewers, many of whom did not realize "that a device with a new "intended use" cannot be found substantially equivalent."[1] Moreover, we strongly urge the FDA to use established public health and scientific standards to determine if a product is substantially equivalent and whether different technological characteristics raise different questions of safety and effectiveness.

In the past, the focus of the 510(k) process has been on letting companies change devices in the name of innovation, not based on public health standards. As a result of this focus on innovation, devices are being cleared as "substantially equivalent" that are in fact substantially different from previous devices. In the absence of clinical trials, it is often not possible to determine exactly what the risks and benefits are likely to be, and it is certainly possible that the newly cleared device is not be as safe or effective as other products on the market. This lack of more stringent criteria for clearance and lack of information about safety and effectiveness potentially costs the medical system (and individuals) billions of dollars each year. Patients may buy or use products that don't work as well as other available products, or they spend a great deal of money to treat health problems that result from the complications of devices that are not as safe as other available products.

Predicate Devices

The 510(k) process has been based on the assumption that a medical device that is "substantially equivalent" to one already on the market does not need clinical trials to determine its safety or efficacy. The definition of substantially equivalent is loosely defined. In 2009, the FDA admitted that "Our Review identified multiple sources of disagreement and confusion about 510(k) standards and practices, including the standards in the FDC Act and FDA's regulations."[2] We strongly urge that the definition be tightened to ensure to better ensure the new products' safety and efficacy.

We agree with the Working Group's assessment of split predicates. The Working Group stated, "The use of a 'split predicate' is akin to combining different attributes of more than one device into a single, nonexistent predicate device, whose risks and benefits are unknown." The group further stated that CDRH should "explore the possibility of explicitly disallowing the use of 'split predicates.'"**Error! Bookmark not defined.** We agree.

We strongly support the Working Group's recommendation that CDRH conduct additional analyses to determine why 510(k) applications that cite more than five predicates are more likely to have a substantially higher rate of adverse event reports.

While this review is underway, the FDA should not allow applicants to cite more than five predicates.

We agree with the Working Group that predicates that are no longer considered safe or effective or that would represent substandard care should not be sufficient for a 510(k) review. The most extreme example is when devices that have been withdrawn from the market due to safety or effectiveness issues are used as predicate devices. This practice clearly put patients' safety at risk and should be prohibited. Moreover, if the new device application is intended to be reviewed as substantially equivalent to a device that is still on the market, if its predicate was withdrawn because of safety or effectiveness, subsequent devices should not be available as predicates. This is necessary because there is often a delay between when a product is cleared and when safety or effectiveness issues become apparent.

However, even if the predicate is not recalled or withdrawn, it may still be substandard because of newer devices or treatments that are available, and in that case should not be considered an adequate predicate.

The Working Group stated that guidance regarding when a device should no longer be used as a predicate should be "well-reasoned, well-supported, and…unintended consequences should be carefully considered." The term "unintended consequences" has been used by industry in the past as an argument against strict standards. They argue that an unintended consequence of strong safety regulations is that it will restrict innovation. However, the unintended consequences of some devices have included injuries and deaths. Those safety issues should be CDRH's main concern.

We support the Task Force's recommendation that CDRH should clearly communicate to industry that the "least burdensome" guidance is not intended "to lower the agency's expectations"[3] on what is necessary to meet statutory standards.

Off-Label Use

We find the Working Group's recommendation regarding off label use to be too vague. It recommends considering a statutory amendment to the FDCA "that would provide the agency with the express authority to consider an off-label use, in certain limited circumstances…Such circumstances would include the availability of compelling evidence that the primary use of the marketed device will be off-label."[1] If CDRH has reason to believe that a primary use is expected to be off-label, then CDRH should insist that the application for clearance or approval be revised to provide scientific evidence that the device is safe and effective for that likely use. That assessment should be strongly influenced by the public health implications, and should influence the FDA analysis of whether the device is high risk, and whether it requires a PMA.

Rescission Authority

The FDA does not have clear authority to rescind clearance once a 510(k) device is cleared. According to FDA's Director of the Office of Device Evaluation, "it is difficult to fix/modify or remove a cleared 510(k)."[4] Rescission authority is essential since these devices are often cleared with little or no data from clinical trials. Rescission authority is especially urgent for devices that were cleared prior to the newly proposed improvements to the 510(k) process.

We support the Working Group's recommendation to issue a regulation defining when CDRH can fully or partially rescind a 510(k) clearance. For example, if new data emerges once a device is on the market that shows the device may be unsafe or ineffective, then CDRH should be able to act on that scientific evidence and rescind the 510(k) clearance. It would be foolish to ignore postmarket data or to tie CDRH's hands and not allow CDRH to act on those data.

The De Novo Classification

The de novo process is intended for lower risk devices that do not have a predicate device. We have strong concerns about the Working Group recommendation that the de novo process should be streamlined and that CDRH should "assure that it is utilized appropriately across the Center."**Error! Bookmark not defined.** In our opinion, the de novo process is a short-cut for devices that should be proven safe and effective through the Premarket Authorization (PMA) process.

Class IIb Devices

We are very concerned about the proposed Class IIb category. Although we favor more stringent review of 510(k) cleared devices, we opposed the Working Group statement that "potential candidates for this device subset may include implantable devices, life-sustaining devices and life-supporting devices." All implantable, life-sustaining, or life-supporting devices should be reviewed through the PMA process. Although there are implantable devices that are not life-sustaining or life-supporting, the failure of an implanted device is often a high-risk event. That is why the law requires that high risk devices be approved through the PMA process. It would be a disaster to lower that standard.

In fiscal year 2010, the FDA charged a standard fee of only $4,007 for a 510(k) submission (and only half that amount for small companies) and $217,787 for an original PMA (one-quarter that amount for small companies)[5] Both are well below the actual cost to the FDA of doing reviews. Since the PMA user fees are hundreds of thousands of dollars below the actual cost of a thorough PMA review, CDRH will continue to lack the resources needed to use the PMA process as often as it should. In addition, the much lower user fees, shorter time-lines, and drastically smaller expense for the company submitting a 510(k) application provide an enormous incentive for companies to pressure the FDA to review their products through the 510(k) process.

There are Class II devices that could benefit from a higher standard of review, such as contact lenses and contact lens solutions, since either can cause blindness or debilitating damage to vision. However, life-sustaining, life-supporting, and implantable devices should be Class III devices and reviewed through the PMA process.

A recent study by the National Research Center for Women & Families found that for the last ten years, the vast majority (nearly 80%) of what FDA considers Class I Recalls—defined as devices recalled because they can cause serious harm or deaths—were 510(k) cleared devices. These recalls have involved millions of devices that were taken off the market, jeopardizing the health of millions of Americans. Class IIb has the potential to dramatically increase those risks. If devices can cause serious harm when they fail such, as implanted devices or devices used to diagnose cancer or other serious diseases, they should not be cleared through the 510(k) process.

Post Market Surveillance

We agree with CDRH's statement that postmarket tools "have important limitations and are not sufficient to serve as a substitute for high-quality premarket review."**Error! Bookmark not defined.**

We agree with the recommendation that CDRH explore greater use of its postmarket authorities" and "seek greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices," as we mentioned in the Rescission Authority section. We also agree with the recommendation that CDRH "implement a unique device identification (UDI) system" and use real world data (anonymous data) as part of a premarket submission for future 510(k)s.

Manufacturing Process Information

We agree that CDRH should clarify when it will withhold clearance on the basis of a failure to comply with good manufacturing requirements. If device makers do not comply with good manufacturing requirements, then their devices should not receive clearance, regardless of whether it is Class I, Class II, or Class III.

Although the FDA states that the "majority of recalls are due to manufacturing and design control problems,"[6] the FDA does not inspect the manufacturing plants of 510(k) products prior to clearance. The agency therefore misses an opportunity to spot contamination, manufacturing flaws, and changes in device design or materials. In addition, key manufacturing information such as engineering specifications about the device design and assurances of on-going quality, may not be included in the 510(k) review process.[7] In contrast, the GAO points out that the agency does inspect manufacturing establishments as part of its review of original PMA submission.[8]

Informed Decision Making

CDRH should provide device makers with clear instructions about its evidentiary expectations. This helps industry by making the process more fair and predictable. In

turn, device makers have an obligation to provide CDRH with all pertinent data about their devices, not just the studies that show the benefits of the device. We support the Working Group's recommendation that CDRH explore the feasibility of requiring manufacturers to provide regular, periodic updates to the Center listing any changes to its devices and if those changes do not require a new 510(k), then clearly explain why the changed device does not need a new 510(k). In fact, we believe that CDRH should ensure that those updates are feasible.

We support the Working Group's recommendation to revise regulations "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."**Error! Bookmark not defined.**

Under quality of submission, the Working Group recommended that a new "guidance should also clearly reiterate the long-standing expectation that 510(k)s should describe any modifications made to a device since its previous clearance."**Error! Bookmark not defined.** If necessary, Congress should consider a change in statute to ensure that.

Third-Party Review

We do not support third-party reviews. CDRH should do all the reviews. The FDA has expressed concerns about the poor quality of third party 510(k) reviews, stating that "most 3rd-party-eligible devices do not have a device-specific guidance [and] accredited parties do not have access to previous decisions/reviews of the device type."[7]

Third-party reviewers have an innate conflict-of-interest. If a device manufacturer considers a third-party reviewer to be too strict, the manufacturer will shop around for a reviewer who is less stringent in the future. Third-party reviewers know this and that provides them with an incentive to not be as strict as they should be. A review process that depends on the company whose product is being reviewed hiring the reviewers is by definition flawed and subject to unacceptable conflicts of interest.

Information Technology

We support the Working Group's recommendations to improve CDRH's 510(k) databases so that they provide more complete and up-to-date device information. All of this information should be publicly available in an easily searchable database that includes a verified 510(k) summary. CDRH should develop a standardized electronic template for 510(k) summaries, which will help to make the database more accurate and complete.

Tools for Quality Assurance

We support the Working Group's recommendation for a new Center Science Council to continuously monitor the 510(k) program's performance and effectiveness, and facilitate knowledge-sharing across review branches to improve internal communication.

Comments on Volume II – Task Force on the Utilization of Science in Regulatory Decision Making (Preliminary Report and Recommendations)

We agree with the Task Force's recommendation that "CDRH take proactive steps to improve the quality of premarket data, particularly clinical data…and develop better data sources, methods, and tools for collecting and analyzing meaningful postmarket information."[3]

We are concerned about the recommendation "to improve knowledge management…by developing a web based network of external experts, using social media technology."[3] How will CDRH ensure the objectivity and lack of conflicts of interest of the external experts? The Task Force stated that CDRH needs to "develop standard business process for the appropriate use of external experts to assure consistency and address issues of potential bias"[3] but it is not clear that will be possible, especially given CDRH's limited resources.

We support the Task Force's recommendation that CDRH establish a Center Science Council with experienced employees and managers from CDRH "to help assure consistency across the Center in responding to new scientific information."[3] However, procedures must be put in place to avoid one person or a few people from dominating the process. Perhaps staff should serve on a rotating basis.

We strongly agree with the Task Force's recommendation 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)."[3] Currently, the standards for clinical trials of devices are inferior to the standards for prescription drugs in terms of number of studies, sample sizes, and methodologies used. We also strongly agree with the recommendation that CDRH expand its efforts "to include clinical trials that support 510(k)s."[3] Too many devices are cleared for the market without solid evidence from clinical trials that the devices are safe or effective.

We agree with the Task Force's postmarket oversight recommendations and that CDRH should conduct a data gap analysis.

Regarding the Task Force's recommendation to streamline its guidance documents process, we support CDRH using the "Level I—Immediately in Effect" option for guidance "intended to address a public health concern."[3] However, we do not support this for lessening the burden on industry, as the Task Force recommends.

We support the Task Force's common-sense recommendation that CDRH develop Standard Operating Procedures in order to respond to new scientific information.

We support the Task Force's recommendations on transparency. We strongly support the recommendation "to release summaries of premarket review decisions to the CDRH Transparency Website."[3]

Summary

As members of the Patient, Consumer, and Public Health Coalition we support most of the recommendations regarding 510(k) improvements but do not support the recommendations regarding third party review or the de novo process. We have also expressed our concerns about the proposed Class IIB category and off-label considerations. Overall, our most important feedback is to urge the CDRH to ensure that changes greatly strengthen existing safeguards to protect the public from products with questionable benefits or unproven safety. We believe that doing so will benefit device manufacturers as well as patients and consumers. We urge CDRH to consider our comments as it works to better fulfill its mission of protecting and promoting the public health.

Breast Cancer Action
Center For Medical Consumers
Community Access National Network (CANN)
Government Accountability Project (GAP)
National Research Center for Women & Families/Cancer Prevention and Treatment Fund
National Women's Health Network
Our Bodies Ourselves
Reproductive Health Technologies Project
The Scientific Integrity Program, Union of Concerned Scientists
THE TMJ Association
Truth in Medicine
WoodyMatters

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[1] Food and Drug Administration (August 2010). CDRH Preliminary Internal Evaluations—Volume I, 510(k) Working Group, Preliminary Report and Recommendations.

[2] Food and Drug Administration (2009). Review of the ReGen Menaflex®: Departures From Processes, Procedures, and Practices Leave the Basis for a Review Decision in Question.

[3] Food and Drug Administration, Center for Devices and Radiological Health (August 2010). CDRH Preliminary Internal Evaluations—Volume II, Task Force on the Utilization of Science in Regulatory Decision Making, Preliminary Report and Recommendations.

[4] Food and Drug Administration, Center for Devices and Radiological Health. (March 2010). Understanding the Premarket Notification (510(k)) Process. FDA's 510(k) Working Group. Presentation to the Institute of Medicine by Donna-Bea Tillman, Ph.D., Director, Office of Device Evaluation.

[5] [4]Department of Health and Human Services, Food and Drug Administration, Federal Register Notice [Docket No. FDA-2009-N-0338] (August 2009). Medical Device User Fee Rates for Fiscal Year 2010. US Government Printing Office Web site.

[6] Food and Drug Administration (February 2010). FDA's 510(k) Workshop: Issues Related to New Technologies and Scientific Evidence presentation by Arleen Pinkos, Scientific Revie3wer, Office of In Vitro Diagnostic Device Evaluation and Safety, CDRH.

[7] Food and Drug Administration (February 2010). FDA's 510(k) Workshop: Issues Related to the Following Types of Submissions: Bundled, 3rd Party, and Submissions which Contain Standards presentation by Barbara Zimmerman, Deputy Director for Premarket Program Management, Office of Device Evaluation, CDRH.

[8] Government Accountability Office (January 2009). Medical Devices: FDA Should Take Steps to Ensure that High-Risk Device Types Are Approved through the Most Stringent Premarket Review Process.

America's Health Insurance Plans (AHIP) – Comment (posted 10/14/10)

FDA-2010-N-0348-0064

America's Health Insurance Plans

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October 4, 2010

Leslie Kux
Acting Assistant Commissioner for Policy
Division of Dockets Management (HFA-305)
Food and Drug Administration,
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Dear Ms. Kux,
Thank you for the opportunity to comment on the Food and Drug Administration's (FDA's) Federal Register notice and request for public comments on the two preliminary internal evaluations, *Volume I: 510(k) Working Group Preliminary Report and Recommendations & Volume II: Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations.* America's Health Insurance Plans (AHIP), the national association representing nearly 1,300 health insurance plans providing coverage to more than 200 million Americans, is pleased to submit these comments on behalf of our members.

GENERAL COMMENTS
AHIP and our member plans applaud the efforts of the FDA, and its Center for Devices and Radiological Health's (CDRH's), in performing and publishing these preliminary evaluations to determine the actions necessary to strengthen and improve how it collects and utilizes current scientific evidence and uses that data to revise the 510(k) premarket approval review process. We also support the Institute of Medicine's (IOM's) ongoing review of the 510(k) process, *Public Health Effectiveness of the FDA 510(k) Clearance Process*, which was requested by the FDA, and are confident that it will provide additional insight into areas of high priority for FDA action that will improve the public's access to safe and effective medical devices.

The 510(k) process was created by Congress in 1976, and was intended to more readily make available devices that are safe and effective, and to foster innovation. However lately, due to several recalls of 510(k) devices associated with complications, questions have been raised regarding whether or not consumers are fully protected under the current process. Given the increasing sophistication of medical technology, the current process may no longer strike the most appropriate balance between device innovation and patient safety. Our members have been, and remain, concerned that complex medical devices have been entering the market through the 510(k) process without a comprehensive clinical evaluation of their safety and long term effectiveness, thereby potentially putting patients at greater risk of adverse events.

The preliminary internal evaluations contain recommendations that, if enacted in their entirety, could lead to significant improvement in the safety of medical devices and a reduction in

potential harm for consumers. The FDA acknowledges, and we concur with, the need to continue encouraging innovation and advancements in technology through access to a more transparent evidence base.

We strongly support the preliminary recommendations stated within *Volume II: Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations* as a step to enhance CDRH's knowledge base. This will greatly assist staff in making meaningful changes to the 510(k) premarket clearance processes. In particular, it is important to strengthen the support FDA provides to manufacturers on appropriate and valid clinical trial development, and for the agency to be transparent in its reviews and approval processes. Information collected during the regulatory decision making process should be shared with all stakeholders including consumers, to assist them in making informed health care decisions.

Our members strongly support the preliminary recommendations provided within these two reports, and encourage FDA to act on them in their entirety. In addition, our members have highlighted specific recommendations where we have provided additional comment.

SPECIFIC COMMENTS

510(k) Working Group Preliminary Report and Recommendations

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.

We support FDA's effort to clarify the definition and revise existing guidance to decrease discrepancies in the use of the two existing terms during the review process. By clarifying "intended use," along with the recommendation to require a more substantial evidence base with each submission, CDRH will be positioned to make more accurate determinations of "substantial equivalence," in which the device seeking 510(k) clearance has the same intended use as the predicate device.

Consider adopting the use of an "assurance case" framework for 510(k) submissions.

We also support implementing the use of an "assurance case" framework for 510(k) submissions. This framework could help demonstrate validity by providing a convincing statement to show that safety and efficacy claims are met and are supported with relevant evidence.

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.

We do not support the recommendation to create a new Class II subset, "Class IIb," which would include higher risk 510(k) devices that would need to be supported by additional clinical and manufacturing data, similar to current Class III device review requirements. As we have stated in our prior comments (March 2010) in response to the docket for Strengthening the Center for Devices and Radiological Health's 510(k) Review Process, given the greater potential for catastrophic results in the event of device failure, there should be stricter criteria and processes in place to appropriately classify medical devices as either class II or III.

FDA also should review all class II devices to determine which devices pose potentially significant safety concerns and reclassify them as class III, as appropriate, requiring the manufacturer to submit a higher level of evidence to demonstrate safety and effectiveness (e.g., class II devices, such as drug infusion devices, intraoperative devices, and medical charged-particle radiation therapy systems). In determining which devices pose a greater risk to patients, thereby requiring a more stringent review of the evidence, our members concur with FDA that potential candidates may include some implantable, life-sustaining devices, and/or life-supporting devices, which present greater risks than other class II device types.

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.

As appropriate, FDA should require more robust levels of post-market surveillance as a condition of clearance for certain devices which have the potential to pose a greater risk to patients. This should also include mandatory adverse event reporting requirements to provide transparent and timely information to physicians, hospitals, consumers and purchasers of health care.

CDRH should continue its ongoing effort to implement a unique device identification (UDI) system.

To assist in the collection of post-market data, our members continue to support FDA in its development and implementation of a unique device identification (UDI) system, as recommended within the evaluation. The creation of a unique device identifier has the potential to reduce medical errors, facilitate recalls, improve reimbursement and inventory control, and reduce product counterfeiting. AHIP strongly supports efforts to more accurately identify and track medical devices and this initiative has the potential to improve the safety and effectiveness of health care for patients, and allow for more accurate post-market surveillance.

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."

Our members strongly support the CDRH preliminary recommendations to develop separate guidance and regulations to provide greater assurance that any comparison of a new device to a predicate is valid and well-reasoned; when a device should no longer be available for use as a predicate because of safety and/or effectiveness concerns; and clarifying the appropriate use of more than one predicate, explaining when "multiple predicates" may be used. Specifically, we encourage CDRH to no longer allow the use of "split predicates," where manufacturers use one predicate as the basis for a comparison for "intended use" and another predicate as the basis for a comparison for "technological characteristics."

As is the case when using split predicates to prove substantial equivalence, the manufacturer is attempting to prove the safety and effectiveness of its new device using a non-existent "device" whose benefits and harms are unknown. This can lead to unintended, and potentially negative, consequences for patients. We support FDA's efforts to advance the public's health by helping speed innovations to make medicines and devices safer and more effective. However, as currently structured, the 510(k) clearance process relies too heavily on the use of historical predicates to prove safety and effectiveness, instead of current scientific evidence.

Take steps through guidance and regulation to facilitate the efficient submission of high-quality 510(k) device information.

Our members strongly support the recommendation that each manufacturer provide regular, periodic updates to CDRH, listing any modifications made to its device, and providing a clear explanation why each modification did not warrant a new 510(k) submission. Existing guidance also should be used to clarify what types of modifications warrant submission of a new 510(k) application; clarify what situations warrant the submission of manufacturing process information as part of a 510(k), and when it is appropriate to withhold clearance on the basis of a failure to comply with good manufacturing requirements.

Develop guidance and regulations regarding appropriate documentation of transfers of 510(k) ownership

The CDRH should update the 510(k) database to include transfers of 510(k) ownership. Documentation pertaining to transfer of ownership should include any substantial changes in the manufacturing environment and clarify that the transfer does not adversely impact it.

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.

We fully support FDA issuing a regulation to define when it is appropriate (and the process) to fully or partially rescind a 510(k) clearance. FDA should be allowed to act quickly to protect patients by removing a potentially faulty and dangerous medical device from the market, based on the latest clinical evidence.

Revise existing guidance to streamline the current implementation of the de novo classification process and clarify its evidentiary expectations for de novo requests.

CDRH should look to revise and strengthen the current implementation of the de novo classification process. There remain concerns that some devices cleared through this mechanism are not of low risk to patients and may require more stringent review. While it is understood that very few devices are classified using the de novo process (16 requests received in 2009), allowing any devices into the market that do not have a predicate device for comparison (and without a more stringent premarket approval application) could leave questions of long-term safety and effectiveness unanswered. FDA should develop a more streamlined approach to de novo reviews, outlining strict data and evidence requirements in light of the lack of appropriate predicate comparison.

We applaud FDA's efforts and the multi-stakeholder review activities underway at the IOM to revise and strengthen the 510(k) and other medical device clearance processes. These efforts to improve how current scientific evidence is utilized within the 510(k) clearance process, while increasing the transparency and availability of the data submitted and reviewed by the FDA, will help ensure and maintain the public's trust that the medical devices available in the market place are dependable and safe.

Thank you for the opportunity to provide these comments.

Sincerely,

Carmella Bocchino
Executive Vice President, Clinical Affairs and Strategic Planning

American Association for Clinical Chemistry (AACC) – Comment (posted 10/14/10

FDA-2010-N-0348-0065

AACC
Improving healthcare through laboratory medicine

2010 SEP 23 A 11:44

September 21, 2010

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

Docket No. FDA-2010-N-0348

Dear Sir/Madam:

The American Association for Clinical Chemistry (AACC) welcomes the opportunity to comment on the Food and Drug Administration's (FDA's) 510(k) Working Groups' Preliminary Report and Recommendations on the Agency's device clearance process. AACC supports the FDA's efforts to clarify and streamline the current 510(k) review mechanism. We believe that clearer, more predictable guidance, in conjunction with needed regulatory reforms, will better serve medical device manufacturers, the health care community, and the public alike.

De Novo Process
The 510(k) Working Group found that "Although there exists an alternative regulatory pathway for devices that lack a clear predicate but whose risks do not warrant class III controls...this pathway, as currently implemented, is inefficient and has not been utilized optimally across the Center." On the basis of this finding, the Group recommends that the FDA "reform its implementation of the de novo classification process to provide a practical, risk-based option that affords an appropriate level of review and regulatory control for eligible devices."

AACC strongly supports the Working Group recommendation. Congress authorized the de novo process to allow the agency to reclassify low risk devices that would automatically be designated as Class III devices, solely because there is no predicate device, as Class I or II. This means that manufacturers, in certain instances, are able to seek clearance through the less burdensome 510(k) process, rather than the more costly and onerous pre-market approval (PMA).

Unfortunately, confusion over evidentiary requirements, along with the length of time associated with Agency review, has discouraged many IVD manufacturers from pursuing this route. In each of the past few years, the Office of Vitro Diagnostic (OIVD) has received only one IVD de novo submission. Since 2005, the length of time for each review has averaged 311 days—50 days longer than the baseline year. We are confident, however, that the number of de novo applications would increase substantially, and the review time decrease, if the process were more clearly defined and predictable.

FDA-2010-N-0348

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The use of the de novo process is particularly important for devices, such as tests for Therapeutic Drug Monitoring (TDM), where consumer demand is often limited, but the potential for improved patient care is significant. Shifting the review of a low volume, low risk test from a PMA to a 510(k) review may make development of a previously unprofitable test, now cost-effective. This change benefits the manufacturer, which now has an incentive to develop and market the test, as well as the patient, who now has access to a valuable test for managing their drug therapy.

Use of Predicate Devices

The Working Group also identified the quality of some predicate devices to be an issue of concern. The panel recommended that "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." AACC agrees with this recommendation. Not all predicate devices are the same. Many are of high quality, but some may be substandard, and possibly not in use anymore. The FDA should ensure that a predicate meets the agency's safety and effectiveness criteria, as well as serves as a valid comparison.

Rescission Authority

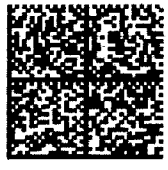
The Working Group recommends "that CDRH consider issuing a regulation to define the scope, grounds, and appropriate procedures, including notice and an opportunity for a hearing, for the exercise of its authority to fully or partially rescind a 510(k) clearance. As part of this process, the Center should also consider whether additional authority is needed." AACC supports this approach. The FDA should have clear, established authority to remove a device from the market if it endangers public safety. Additionally, its important for manufacturers to understand what circumstances may trigger an agency action and what options are available for appeal.

By way of background, AACC is the principal association of professional laboratory scientists--including MDs, PhDs and medical technologists. AACC's members develop and use chemical concepts, procedures, techniques and instrumentation in health-related investigations and work in hospitals, independent laboratories and the diagnostics industry worldwide. The AACC provides international leadership in advancing the practice and profession of clinical laboratory science and its application to health care. If you have any questions, please call me at (919) 966-3724, or Vince Stine, PhD, Director, Government Affairs, at (202) 835-8721.

Sincerely,

Catherine A. Hammett-Stabler, Ph.D., DABCC, FACB
President, AACC

AACC
Improving healthcare through laboratory medicine
1850 K Street, NW, Suite 625
Washington, DC 20006-2213



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Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations; Availability for Comment

At http://www.regulations.gov/ Comments posted relating to Docket No. **FDA-2010-N-0348**

John William Schaefer - Comment (Posted 8/09/10)

FDA-2010-N-0348-0002

The current 510(k) process encompasses a wide range of risk levels, extending from non-patient-contact, disposable plastic equipment-contamination-prevention covers to highly critical invasive and diagnostic systems. The revised process should be multi-tiered based on risk categorization and risk analysis, with higher risk, highly critical devices subjected to considerably strengthened evaluation. Filing fees also should be scaled by risk tier so that sufficient funding is available to conduct those more intensive evaluations of higher-risk devices. The existing Product Code system is overly complex, based on conflicting rationales, duplicative in multiple areas, and broadly inconsistent with rest-of-world classification approaches in ways that are not justifiable based on safety and effectiveness. Some proportion of the dysfunctionality of the current 510(k) system comes from the workload resulting from low-risk Class II devices. Perhaps it would make sense to shift some Product Codes to Class I when they do not involve patient contact or more broadly when they are low risk. Or, perhaps it would make sense to move to a harmonized approach, to create a better foundation for the revised 510(k) system.

Deanna J Carter - Comment (Posted 8/09/10)

FDA-2010-N-0348-0003

There are a number of terms that need to be clarified: "intended use," "indications for use," "technological characteristics," etc. It was extremely disappointing that reviewers within CDRH have such differing thoughts/opinions on the definition of these terms and their application. It lends to the ongoing hope of "I hope I get a good reviewer." Industry should not hope to have a "good" reviewer but rather, industry should know exactly what is expected and required of them. Likewise, industry should know what to expect from FDA. It is also disappointing that FDA subcumbs to political pressures to clear/approve devices. Grant it, this is not the norm; however, there should be clear requirements and everyone should be required to satisfy them. Although it is a great idea, asking mfg's to provide addt'l data to FDA with regards to changes and the justification for not submitting supplemental or new 510ks will be extremely burdensome. Will the list of changes just merely be submitted to FDA and get lost in a black hole or will there be a response time in which FDA will respond with "proceed" or "halt production?" I recommend that no FDA decision is required to continue production/sales. In fact, I recommend that mfg's keep a list of changes and their corresponding justifications for not submitting a supplemental or new 510k on file for FDA to review while auditing the site. This eliminates the need for "random" reviewers to get up to speed with the company, background, product, etc and promotes the relationship between the Mfg and the Mfg's FDA auditor. Ultimately, this would save FDA time and would create value whereas sending in a list to FDA to a random reviewer is burdensome, time consuming, and potentially disruptive to the commerical/patient market.

Deanna J Carter - Comment (Posted 8/09/10)

FDA-2010-N-0348-0004

A delineation between class II devices to include "IIa" and "IIb" to aide in determining which devices require clinical data to support a 510k will be extremely value added. Will devices that are IIb (presumably requiring clinical data) be required to have clinical data if the predicate device was approved under the new "IIb" class? In other words, if the predicate device provided addt'l clinical data, would the new device be required to submit even more clinical data? Clarification around those requirements would be appreciated. Schematics, pictures, devices, or visits to the device (in case of large devices), should be employed. However, zero of this data should be available to the public. However, if this is implemented, it seems reasonable to expect FDA to require this of everyone, not just those companies that can easily transport a device. In other words, just because a visit to the company may be required, this should not remove or lessen the requirement of seeing a device. Either devices are required or they are not. Clear guidance on expectaions / requirements of the 510k submission would be highly value added. Periodic reviews of the 510k cleared devices is something that should be employed. Perhaps this is something that is performed during a Mfg's audit. The examples in the report aided greatly in conveying key concepts. Examples such

as these should be employed more often in FDA's guidance. FDA guidance is sometimes perceived as being law to some reviewers and industry. Tighter controls need to be implemented to streamline this thought into either they are requirements or they are not. The"c" in cGMP can be misleading and fear inspiring. One cannot know what one does not know. If FDA reviewers do not have a clear understanding of what the requirements are and what the requirements ought to be, the MFG is left in the dark. Guidances need to be made law if FDA is going to expect them to be implemented.

Deanna J Carter - Comment (Posted 8/09/10)

FDA-2010-N-0348-0005

FDA should employ a forum or forum-like platform where questions / concerns / best practices are available for the public. It should of course be monitored by FDA and include the caveat that items contained in the forum are general guidelines and are intended to aide. However, the forum or "forum-like platform" is not intended to replace the regulations currently in place. This would aide in determing current thinking of FDA and a "non-fear" inspiring method of communicating with the FDA. This would aide not only mfgs but the public as it would add transparency to the process and clarify some of the not so clear requirements.

National Venture Capital Associate – Comment (posted 10/06/10)

FDA-2010-N-0348-0006

Indiana Medical Device Manufacturers Council (IMDMC) – Request for extension (posted 10/6/10)

FDA-2010-N-0348-0007

RE: Docket No. FDA-2010-N-0348 Dear Mr. Desjardins, On behalf of 60 medical device manufacturers and associated business members of the Indiana Medical Device Manufacturers Council (IMDMC), we respectfully request a 30-day extension of the comment period for the docket referenced above ? CDRH 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations. Indiana is one of the world leaders in the medical device industry. In fact, according to the U.S. Census, Indiana is the 2nd largest state in the value of medical device products shipped. A wide variety of medical device manufacturers employ approximately 19,950 Hoosiers across the state, with a payroll of more than $1 billion ranking Indiana 7th in the nation in terms of medical device sector employment. The IMDMC supports the efforts of FDA to assess and improve the 510(k) process. We welcome the opportunity to comment on the findings and recommendations documented in the CDRH Preliminary Internal Evaluations reports and are working to draft comments that we believe the CDRH will find helpful. Given the length of the reports and the numerous recommendations reflecting significant new requirements for many of our members, we are concerned that the published comment period does not allow adequate time to draft comments reflecting our members? perspectives. Therefore, we request a 30-day extension to the comment deadline of October 4 to allow us the time needed to provide constructive feedback. Thank you for your consideration of our request. Sincerely, Danelle Miller IMDMC President

Consumers Union – Comment (posted 10/6/10)

FDA-2010-N-0348-0008

Thom Davis – Comment (Posted 10/6/10)

FDA-2010-N-0348-0009

Recall that the discussion is about devices and not pharma--no "c". QSR is the defined expectation. Concur about most of the rest, though. One thought, in vitro diagnostic devices are medical devices by definition...makes little sense to "go look at them".

Advanced Medical Technology Association (AdvaMed) – Comment (posted 10/6/10)

FDA-2010-N-0348-0010

SCC Soft Computer – Comment (posted 10/06/10)

FDA-2010-N-0348-0011

Liesl Lanell Wright – Comment (posted 10/06/10)

FDA-2010-N-0348-0012

Every single device that is approved by the FDA should be carefully reviewed for safety before the public is exposed. Many people have been harmed by medical devices approved by the FDA, as the MAUDE database can attest. These actual reports represent a small minority of those people who have been harmed by FDA approved medical devices. Cosmetic devices in particular are marketed to an unsuspecting public as "non-invasive" alternatives to surgery. In actuality, these devices are powerful enough to burn and seriously injure. Now the American Society for Dermotologic Surgery has launched a campaign to warn consumers of the potential dangers of cosmetic devices. Yet the FDA continues to allow these devices on the market with little effort to protect public safety.

RTI Biologics, Inc – Comment (posted 10/6/10)

FDA-2010-N-0348-0013

BioMet - Comment (posted 10/06/10)

FDA-2010-N-0348-0014

Evergreen Research, Inc – Comment (posted 10/6/10)

FDA-2010-N-0348-0015

BlueCross BlueShield Association – Comment (posted 10/06/10)

FDA-2010-N-0348-0016

American Society for Radiology Oncology (ASTRO) – Comment (posted 10/06/10)

FDA-2010-N-0348-0017

Tethys Bioscience, Inc. – Comment (posted 10/6/10)

FDA-2010-N-0348-0018

Galil Medical, Inc – Comment (posted 10/06/10)

FDA-2010-N-0348-0019

Abbott Laboratories – Comment (posted 10/06/10)

FDA-2010-N-0348-0020

Norman Frederick Estrin, PhD. – Comment (posted 10/06/10)

FDA-2010-N-0348-0021

The FDA should consider implementation of a system analogous to the OTC Drug Monograph system for class IIa medical devices. Such Monographs would include descriptions, labeling options, performance testing requirements, etc. Predicate devices may no longer be necessary for class IIa devices. In this way, medical devices that meet the parameters set by the FDA for a product type (perhaps as defined by product codes) could be marketed if they meet the monograph without pre-submission requirements or with a simple pre-market notification that the device meets the monograph and will be marketed shortly. If the device has differences from the monograph that could impact safety and effectiveness, supporting data would be submitted with the pre-market notification for expedited review. CDRH could use its guidance documents as a start in developing monographs. These could be prepared with industry input and frequently updated to keep up with innovations in technology. FDA should consider inviting device companies to prepare draft monographs through their trade associations for submission to the FDA. CDRH should study the successes and failures of the OTC Drug program and take all necessary steps to avoid potential problems of inhibition of developing new technologies because of rigid, inflexible monographs, slow progress in developing and finalizing monographs and internal FDA barriers to incorporating innovations in technology into monographs. A final General comment: Much of the 510(k) Working Group report is commendable but it is of much concern that some recommendations, if implemented, could place significant additional paperwork and administrative burdens on the smaller companies of the medical device industry and raise costs sufficiently as to inhibit introduction of new devices. FDA's User Fee authority should not be used for unlimited growth of the FDA at the expense of the industry and patients that would benefit from medical devices.

Japan Industries Association of Radiological Systems – Comment (posted 10/06/10)

FDA-2010-N-0348-0022

American Association for Justice (AAJ) – Comment (posted 10/06/10)

FDA-2010-N-0348-0023

Roche Diagnostics – Comment (posted 10/06/10)

FDA-2010-N-0348-0024

Eli Lilly and Company – Comment (posted 10/14/10)

FDA-2010-N-0348-0025

Novo Nordisk, Inc. – Comment (posted 10/14/10)

Please see attached comment letter

FDA-2010-N-0348-0026

Stephen L. Ferguson – Comment (posted 10/14/10)

Attached are comments submitted on behalf of Cook Group Incorporated to FDA 510(k) Working Group and Task Force on Science Utilization.

(no comments posted at this point)

FDA-2010-N-0348-0027

Indiana Medical Device Manufacturers Council (IMDMC) – Comment (posted 10/14/10)

See attached file(s)

FDA-2010-N-0348-0028

Massachusetts Medical Device Industry Council (MassMEDIC) – Comment (posted 10/14/10)

FDA-2010-N-0348-0029

Anonymous – Comment (posted 10/14/10)

FDA-2010-N-0348-0030

Proposal Addressing Obtaining Predicate Devices for 510k Testing FDA frequently requires submitting companies to complete predicate testing to prove substantial equivalence to another approved product. If the submitting company isn?t the owner a suitable predicate device, how is the submitting company suppose to obtain the predicate device? The devices are controlled by prescriptions as well as the predicate device companies not allowing competitors access to their products. These constraints make it difficult and sometimes impossible to get predicate devices for mechanical testing. Companies are left to their own to obtain the predicate devices by whatever means are possible. One common place to get device predicates is referred to as the "medical device black market" where you can get your predicate for the "right price". This market is being driven by the FDA's requirements for predicate testing along with the lack of a procurement process for medical devices for the purposes of predicate testing and submitting 510ks. Devices are being over ordered by surgeons, hospitals, and 3d party distributors and then resold for up to 5x the cost to submitting companies. Currently this is the primary predicate pathway. Is this legal? Ethical? A pathway must be created to obtain predicate devices on the US market. This pathway may make approved devices may be vulnerable towards competitors learning the intricacies that make them work, and then using such knowledge to make better devices, but so what. IP is protected by patent claims, not inventory control so a device can go from the shelf into a patient. Please remove the black box around these devices which will create a pathway for the industry to obtain, test, and learn from them. Ultimately we will have better products produced at lower costs and improved patient care in the end. Or publish the FDA benchmark data so that the industry isn?t required to obtain predicates to test.

Alliance for Aging Research – Comment (posted 10/14/10)

FDA-2010-N-0348-0031

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

FDA-2010-N-0348-0032

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

FDA-2010-N-0348-0033

Covidien – Comment (posted 10/14/10)

FDA-2010-N-0348-0034

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

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

No comments attached

FDA-2010-N-0348-0035

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

FDA-2010-N-0348-0036

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

Please take these comments into consideration. Thank you.

FDA-2010-N-0348-00637

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

FDA-2010-N-0348-0038

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

FDA-2010-N-0348-0039

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

FDA-2010-N-0348-0040

To Whom It May Concern: BIOCOM leads the advocacy efforts of the Southern California life science community with more than 550 dues paying members including biotechnology, medical device, and biofuel companies, universities and research institutions, as well as service providers. In our mission of providing feedback and communication between the industry and regulators, we are writing in response to the FDA?s CDRH Internal 510(k) Working Group Report, Docket No. FDA-2010-N-0348, "Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations; Availability for Comment." The proposed recommendations in the report include many changes to the 510(k) process that could impact the development and clearance of medical devices. There are areas where BIOCOM feels there is good alignment with the industry; for example, BIOCOM agrees with the approach CDRH's working group recommends for reforming the ?De Novo? process. This includes steps to encourage pre-submission engagement between submitters and review staff, recommendations related to sound changes that streamline and clarify the expectations for de novo requests, what information should be submitted to determine eligibility for de novo classification, and recommendations which would establish baseline device-specific special controls. BIOCOM agrees the changes CDRH has proposed will help address inefficiencies and improve predictability. Although the spirit of many of the proposed recommendations included in the CDRH Internal 510(k) Working Group Report appear to attempt to address what steps CDRH might take to improve the 510(k) program, a concern equally shared by the industry, BIOCOM has strong objections and concerns related to the following recommended changes: "Off-Label Use" BIOCOM has strong objection to the working group?s recommendation which sugges

BIOCOM – Comment (posted 10/14/10)

FDA-2010-N-0348-0041

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

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

FDA-2010-N-0348-0042

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

FDA-2010-N-0348-0043

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

FDA-2010-N-0348-0044

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

FDA-2010-N-0348-0046

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

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

FDA-2010-N-0348-0045

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

FDA-2010-N-0348-0047

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

See attached

FDA-2010-N-0348-0048

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

FDA-2010-N-0348-0049

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

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

FDA-2010-N-0348-0050

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

FDA-2010-N-0348-0051

CONNECT – Comment (posted 10/14/10)

FDA-2010-N-0348-0052

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

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

FDA-2010-N-0348-0053

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

FDA-2010-N-0348-0054

United Spinal Association – Comment (posted 10/14/10)

See attached file(s)

FDA-2010-N-0348-0055

LifeScience Alley – Comment (posted 10/14/10)

FDA-2010-N-0348-0056

Coalition of Medical Device Manufacturers – Comment (posted 10/14/10)

FDA-2010-N-0348-0057

National Association of Manufacturers and U.S. Chamber of Commerce – Comment (posted 10/14/10)

FDA-2010-N-0348-0058

Advanced Medical Technology Association (AdvaMed) – Comment (posted 10/14/10)

FDA-2010-N-0348-0059

ProXimal Ventures – Comment (posted 10/14/10)

FDA-2010-N-0348-0060

Quintiles Consulting – Comment (posted 10/14/10)

Submitting on behalf of Quintiles Consulting, Medical Device Development Group

FDA-2010-N-0348-0061

King & Spalding LLP – Comment (posted 10/14/10)

FDA-2010-N-0348-0062

Patient, Consumer, and Public Health Coalition – Comment (posted 10/14/10)

FDA-2010-N-0348-0063

America's Health Insurance Plans (AHIP) – Comment (posted 10/14/10)

FDA-2010-N-0348-0064

American Association for Clinical Chemistry (AACC) – Comment (posted 10/14/10

FDA-2010-N-0348-0065

National Venture Capital Association

October 4, 2010

Jeff E. Shuren, M.D., J.D.
Director
Center for Devices and Radiological Health
Food and Drug Administration
White Oak Building 66
10903 New Hampshire Avenue, Room 5429
Silver Spring, MD 20993

Re: NVCA's comments to Docket no. FDA-2010-N-0348, FDA's recommendations to improve oversight of medical devices

Dear Dr. Shuren,

The National Venture Capital Association (NVCA) appreciates the opportunity to comment on FDA's recommendations to improve oversight of medical devices provided in two preliminary reports, CDRH Preliminary Internal Evaluations-Volume 1 and CDRH Preliminary Internal Evaluations Volume II. We look forward to working with you and the agency to accomplish the agency's stated mission to "*make available to consumers devices that are safe and effective, and to promote innovation in the medical device industry.*"

NVCA hopes that a comprehensive review of the 510(k) framework may alleviate some of the current innovator frustrations with the medical device review process to allow the agency to meet its stated goals. The result would be improved, science-based regulation; enhanced health and quality of life; the creation of new high-skill, high wage jobs, and enhanced global competitiveness in the United States.

NVCA is comprised of more than 400 member firms and is the premier trade association representing the U.S. venture capital industry. NVCA's mission is to foster greater understanding of the importance of venture capital to the U.S. economy, and to support entrepreneurial activity and innovation. The NVCA also represents the public policy interests of the venture capital community, strives to maintain high professional standards, provides reliable industry data, sponsors professional development, and facilitates interaction among its members.

Innovation is a hallmark of the American economy and venture capital investment drives innovation, especially in the life sciences sector. From 1998 to 2008, venture capital investment in the life sciences sector more than doubled from $3.5 billion to $8 billion.

FDA-2010-N-0348 C

Moreover, venture capitalists play a major role in bringing innovative and clinically useful technologies and therapies to market because VCs are focused on early-stage, high-risk technologies. Venture capitalists fund research and development which is considered too high risk for more traditional funding sources and VCs fill the financial void from discovery to development of novel medical innovations.

Our comments today are focused on the recommendations that will have the greatest impact on the advancement of medical innovation. These comments respond to the significant proposals made by the FDA's 510(k) Working Group, cutting conceptually across recommendations presented in Dr. Shuren's Summary Memo. As a result, we have categorized our responses according to the general subject posed by the report.

Our detailed comments are contained in the attached appendix.

Topic	Comment Page
Off label Use	**3**
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***De Novo* Process**	**7**
Quality of Clinical Data	**8**
Access to External Expertise	**9**
Applying a Predictable Approach to Determine the Appropriate Response to New Science	**10**

The NVCA looks forward to working with the agency to develop and implement improvements in the review process for innovative medical technologies.

Best Regards,

Kelly Slone

Kelly Slone
Director, Medical Industry Group
National Venture Capital Association
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Off label Use

The NVCA strongly opposes any amendment to section 513(i)(E) of the Federal Food, Drug and Cosmetic Act (FFDCA) that would authorize FDA to consider an "off label" use to be part of the proposed 'intended use' of a device in a 510(k) review. This proposal would radically alter the 510(k) system, lead to enormous additional burdens on sponsors, create vast uncertainty and unpredictability in reviews, and undermine one of the most important processes for development of medical innovation — the ability of physicians to explore novel uses of existing device technology in their own practices.

The Working Group argues that amending section 513(i)(E) is desirable in cases in which it believes the device may be intended for a use other than as described in the proposed labeling and that it should be allowed to evaluate this 'use' and not the proposed labeled use, in its 510(k) review. It further suggests that such uses may be harmful or not effective and that therefore, it should be permitted to deny clearance to such devices even if the proposed on label use would be perfectly permissible.

NVCA strongly disagrees. The current 510(k) system— as are the Agency's statutory mission and specific statutory authorizations for new drug and device reviews — is based upon balancing the need to protect the public against the marketing of unsafe or ineffective products against the equally vital need to foster innovation so that new safe and effective therapies, diagnostics, and cures are available to the public. While the use of an unsafe device can harm the public health, it is equally true that barring or delaying the availability of novel products can be just as harmful.

It is critical that the FDA account for both sides of this risk-benefit calculus in formulating its policies. Yet there is no mention of these considerations at all in the Working Group proposal, let alone the extensive cost benefit analysis that one would expect to accompany such a significant change to current policy. This is a significant departure from the Agency's mission and authorities under the FFDCA, which clearly mandates that it balance barriers to innovation, including those that manifest in inefficient or outsized FDA premarketing clearance and approval policies, against fostering and promoting innovation.

Congress intended the FDA to balance risks with benefits to require a reasonable assurance of safety and effectiveness. Whenever necessary, Congress has intervened to instruct FDA to consider these tradeoffs explicitly. It is critical that the FDA recognize that many pivotal judgments about risks, benefits, and innovation were made by Congress over thirteen years ago in enacting the Food and Drug Administration Modernization Act (FDAMA, Pub. L. 105-115).

In 1997, the FDA was instructed to consider the "least burdensome" methods for sponsors to demonstrate safety and effectiveness. As the legislative history of FDAMA makes clear, this directive was necessary because resources are constrained and that requiring levels of evidence above the minimum reasonably necessary to meet the statutory burden of approval was wasteful and would hinder innovation.

More importantly, under FDAMA, Congress also directly addressed the issue that the Working Group raises regarding the intended use of a submitted device, and directed the Agency to adopt an entirely different policy. Having considered and rejected the policy endorsed by the Working Group, Congress amended section 513(a)(3)(E) of the FFDCA and instructed the FDA to determine intended use "upon the proposed labeling submitted in a report for the device under section 510(k)." Discretion was afforded to the Director of the Center for Devices and Radiological Health (CDRH) to require a labeling statement regarding a use "not identified in the proposed labeling" provided there was a reasonable likelihood that the device would be used for such use, which could cause harm.

Finally, Congress undertook to direct the Agency further under section 214 of FDAMA by establishing in statue a clear demarcation between the Agency's responsibilities and interference in the "practice of medicine." Congressional intent was clear: the use of cleared or approved devices by licensed physicians exercising their best judgment about their patients' best interests leads to enormous innovation which simply could not take place if such creativity and progress were paid for and managed in its entirety by sponsors and constrained by burdensome FDA regulation.

This policy judgment enshrined a firm grasp of the impossibility of requiring any sponsor to test and study its device for all conceivable potential uses. In many cases, it might not even think of such uses. The potential market for such use might be too small to justify the large cost of regulatory approval. In many other cases, the new use might require experimentation with the concomitant use of other technology or even the wholesale revision of the healthcare delivery system. In other cases, the learning curve of the medical community is extremely long and gradual, and beyond the economic life of a potential innovator sponsor

To ensure that novel uses and products continued to flow through the FDA's oversight, Congress balanced the protection and endorsement of 'off label use' by physicians with sharply constraining the promotion and marketing of off-label product uses by sponsors under section 401 of FDAMA. Nowhere is there a clearer and careful balance of equities — of the need for innovation and experimentation against overuse and marketing of unproven technology —than the aforementioned statutory mandates crafted by Congress in FDAMA.

In contrast, the Working Groups proposal would greatly reduce this indispensable source of innovation for the following reas ons:

1. It would make the 510(k) process completely unpredictable. In essence, every reviewer would be allowed to speculate on potential off label uses for a device and require that evidence supporting such use be produced by the sponsor. It would be impossible to predict this in advance.
2. It would add enormous expense to the 510(k) process as sponsors would need to gather data on such potential off label uses in advance of FDA submissions in order to both asses the likelihood of such inquiries or to be able to respond.
3. The expense would be even greater if sponsors are required to gather safety and efficacy data for such uses as a condition to clearance. As discussed above, one

of the reasons why we allow off label use in the first place is in cases where markets are too small to justify such expense or other developments. In both of these cases, forcing these uses 'on label' would simply shut down all innovation in the area.

In seeking to effectively overturn the balanced policy judgments reached in FDAMA, the FDA has not made a compelling case that regulation of 'off label' use is necessary at all. The Working Groups statistics on higher rates of Medical Device Reporting (MDR) adverse events for 510(k) approved as SE with limitations might be due to the fact that such devices are simply inherently more complicated or risky, representing an obvious selection bias. Even if the higher rates of MDR's associated with these devices are related to their 'off label' use, it may be that the off label use is simply associated with higher complication rates because of the nature of the underlying condition.

NVCA strongly cautions the FDA from undercutting carefully crafted statutory authorities enacted under FDAMA and understating its already substantial authority to prevent off label device promotion by sponsors. Absent clear and compelling evidence, the FDA should respect current law and seek to preserve the experimentation that leads to much of the most important medical device innovation.

Split Predicates

NVCA Position
The NVCA believes that the Working Group's rejection of "split predicates" in substantial equivalence justifications could stifle a major source of innovation under the current system of 510(k) premarket clearance. The Working Group in effect attempts to identify problems with devices that were cleared by split predicates, but fails to effectively document major issues caused by such substantial equivalence decisions.

Value of Split Predicates

Split predicates have been traditionally used as a method to clear an existing technology to address needs and intended use that are not characteristic of the particular technology. It is commonly accepted throughout industry, the medical community, and in regulatory systems worldwide that the use of a technology for one intended use can be illuminative to how it will perform for another use. Contrary to the Working Group's assertions, split predicates can and have provided a reliable indication of the risk/benefit profile of the application of a technology. This background information, along with additional data addressing open questions of safety and effectiveness, has long provided a reliable basis for premarket clearance of Class I and II devices in the United States.

For example, split predicates were a critical part of the substantial equivalence determinations for the Acclarent sinus dilatation balloons and the Kyphon vertebral dilatation balloons. Both devices were predicated upon general surgical dilatation balloons as a technological predicate even though they did not possess the specific indications for use that the devices were cleared under.

Root Cause Problems in Application of Technological Changes

Since the establishment of the 510(k) process, the FDA has used multiple mechanisms to try to allow new technology to be cleared, including split predicates and the *de novo* 510(k) process.

Unfortunately, the intended use Working Group's own data demonstrates widely discrepant conclusions between reviewers and branch managers on questions of when a specific new technology poses new types of questions of safety and effectiveness, which leads to a determination that a device is not substantially equivalent (NSE) to the intended use predicate device. Yet as critical as this judgment is for a new device, the Working Group's own survey demonstrated that the current process allows no predictability as to whether a technologically innovative device will be regarded as NSE to its intended use predicate.

Table 5.3. Reviewer Survey Responses "New Types of Safety or Effectiveness Questions"

Question: Which of the examples below represent a new type of safety or effectiveness question(s)? (Select all that apply.) **Option**	**Reviewers** % Selected (#)	**Managers** % Selected (#)
A. An ultrasound device cleared for imaging of a fetus has a new feature to assess the stiffness of coronary arteries to determine if there is coronary artery disease.	87.0% (160)	85.7% (18)
B A surgical device cleared to cut and ablate tissue using RF (radiofrequency ablation) is the predicate for a microwave thermotherapy system to necrose tissue.	71.2% (131)	52.4% (11)
C. A manual medical device such as a colonoscope is redesigned to be fully automated.	78.3% (144)	38.1% (8)

Example B above is especially poignant since this exact predicate construction occurred in 2000 when microwave ablation was first applied to cardiac surgery within the 510(k) process. No matter which group is correct in its interpretation, the Working Group's data documents a process that generates highly unpredictable results.

Another potential mechanism for dealing with the new application of an existing technology to an Intended Use could be the *de novo* process. This process has the potential to evaluate each novel combination of an existing technology and intended use on its own merits, without reference to specific predicates. However, given that current timelines for the clearance of a device through the *de novo* process exceeds 16 months, this mechanism does not afford substantial potential for improvement.

Conclusion

The Working Group was unable to document any real risk due to the use of split predicates.

Moreover, in failing to provide an alternative to the use of split predicates in substantial equivalence determinations, which is currently critical to continued innovation in medical devices, the Working Group appears willing to contemplate significant impairment of current device clearances without foreseeable and necessary improvement.

Today, the use of split predicates is one of the last remaining viable processes to newly apply an existing technology to an existing intended use. Banning the use of split predicates would obstruct some of the most useful and prolific sources of innovation in medical device development. The NVCA encourages the FDA to continue to allow sponsors and investigators to look at the current application of a technology and glean the pertinent information that describes the risks and benefits of a technology. While the existence of a technological predicate is not wholly definitive of the risks and benefits of a new technology applied to an old intended use, it nonetheless provides better guidance to the question of whether "new types of questions" are raised by the new technology application than current Agency guidance to sponsors.

De Novo **Process**

NVCA Position
NVCA believes that the medical device industry needs a robust and efficient *de novo* process, or analogous process, for granting market clearance to moderate risk devices that do not have a clear predicate in the current 510(k) system.

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

Root Cause Problems in Application of Risk Assessment and Device Classification
Because of deficiencies in the statutory framework for allowing the introduction of innovative low and moderate risk medical devices into the market place through the 510(k) process, the FDA introduced the *de novo* 510(k) process to permit the premarket clearance of lower risk devices with no clear predicate.

As the Working Group noted, the process necessary to secure a "Not Substantially Equivalent" (NSE) determination from the FDA is lengthy and unnecessary. In most cases both the sponsor and the Agency know a device has no adequate predicate. The burden to the Agency of developing specific special controls for each *de novo* device nearly stops the progression of an application through the Agency.

NVCA recommended solution.
Nonetheless, a modified *de novo* process could provide one of the best and most immediate mechanisms for the clearance of innovative devices. The NVCA supports a modified *de novo* process that will provide the FDA the flexibility it needs to assure the safety and effectiveness of an innovative device. Such a process would entail the self-determination by the sponsor, or the rapid determination by the Agency, of whether a device can progress through a modified *de novo* process. By sharing risk assessment

criteria with the public, the Agency can enable sponsors to prepare assessments and facilitate the determination that the device is of low to moderate risk and therefore classifiable as a Class I or II medical device. Such sponsor self-determination could be linked to a baseline assumption that clinical data would be required to support premarket clearance.

The NVCA supports the Working Group's recommendation that, in place of formal device-specific special control guidelines, adequate controls may include "the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines and other appropriate actions as [FDA] deems necessary." Such alternative "special controls" have been found to be adequate for devices that have progressed through the traditional 510(k) process. There is nothing so unique about the safety and effectiveness of a *de novo* device that would reduce the appropriateness of these alternative "special controls."

Quality of Clinical Data

NVCA agrees with the Agency that the clinical trial design and agreement process for IDEs needs substantial improvement.

The Task Force report states:

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

NVCA believes that the one of the most significant sources of regulatory delay in developing innovative medical devices is in the IDE and clinical trial protocol design phase. As the Agency's data confirms, the IDE approval cycle is lengthening substantially and the rate of approval with conditions and outright non-approvals is increasing.

We believe that the trend is actually substantially worse than this from a public health perspective. Because the data presented is an average over all IDE submissions, it masks the more disturbing trends relating to IDE approvals for the most novel and potentially important device submissions. It is likely that lengthy delays associated with just a few very novel submissions are the root cause of the overall trend.

Submissions relating to novel technology or indications often raise new questions of safety and effectiveness and also may not have precedential approval pathways to follow as a guide.

In addition, such submissions may involve domain knowledge that does not exist within the agency, or even among external advisors.

All our members have reported that this problem requires immediate attention.

NVCA strongly recommends the adoption of a process for the special review of novel and important device submissions that would address problems such as this. As a first step, we suggest that the new Science Council be tasked with oversight of these types of submissions and be available for interactive and real time settlement of disagreements, as they arise.

Access to External Expertise

NVCA agrees that FDA should substantially expand and improve the process by which it accesses external experts.

The Task force reports:

> The Task Force recommends that CDRH, consistent with the Center's FY 2010 Strategic Priorities, develop a web-based network of external experts, using social media technology, in order to appropriately and efficiently leverage external expertise that can help Center staff better understand novel technologies, address scientific questions, and enhance the Center's scientific capabilities.
>
> The Task Force further recommends that CDRH assess best-practices for staff engagement with external experts and develop standard business processes for the appropriate use of external experts to assure consistency and address issues of potential bias. As part of this process, the Center should explore greater use of mechanisms, such as site visits, through which staff can meaningfully engage with and learn from experts in a variety of relevant areas, including clinical care. In addition to supporting interaction at the employee level, the Center should also work to establish enduring collaborative relationships with other science-led organizations.

NVCA agrees with these recommendations and would add the following:

1. FDA should be allowed to grant expedited and broad conflict of interest waivers to allow interaction with external Consultants with particular expertise in subject matter not easily accessible otherwise. Sponsors should be allowed to agree to permit FDA access to such consultants under strict non-disclosure agreements that might encompass the consultants interaction with the FDA (i.e., the consultant would not be allowed to disclose the substance of such interactions even with the sponsor.)
2. We believe the Center should work to establish other collaborative and enduring relationships with other groups in addition to science-led organizations.

For example, the venture capital community finances, manages, and often initiates most of the novel medical device development in the US. We think it would be in the interest of the Center to establish collaborative relationships with the venture community and entrepreneurs with appropriate recognition and management of conflicts of interest.

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

NVCA applauds the Task Force Proposal to establish a Center Science Council. We believe that such a Council, if properly staffed and resourced, has the potential to address many of the problems raised in the Task Force report as well as address other urgent problems not raised in the report.

Our specific comments are as follows:

1. We believe it is critical that the Science Council promulgate and then monitor clear rules concerning when new science will justify a change in an established or ongoing regulatory path.

Our major concern about such changes is that they undermine the value of predictability, which, in turn, raises the risks in developing new technology. Frequent changes to precedent, or changes to trial design after a trial has begun, are enormously expensive, disruptive and greatly reduce the willingness of all sponsors to fund innovation. Thus, such changes must be weighed not just against the specific risk and benefit of the case in question, but against the vast increase in lack of predictability and therefore perception of risk, for the entire device development ecosystem as a whole. Such changes must be weighed against their potential systemic impact and should be permitted or required only when the need for such a change is compelling and overwhelming.

For example, the Science Council must prevent the 'fine tuning' of risk benefit as trials progress and new information is generated. Real time changes should not be permitted just because a new endpoint might be 'better than' the existing endpoint if the existing endpoint is still valid. On the other hand, safety concerns that were unknown previously might justify real time changes, but again, these must be weighed against the potential disruption of the entire innovation ecosystem, in general.

Our specific recommendation is that the Science Council should permit real time or retrospective changes based upon safety only when the safety evidence is substantial and, if confirmed, would likely reverse the risk benefit hypothesis of the trial.

In the case of effectiveness, such changes should be permitted only when the evidence is clear and, if not incorporated, would reverse the risk benefit hypothesis of the trial.

2. We believe that Science Council's mandate should be specifically expanded to include oversight of the approval of Novel Technology.

The NVCA has long argued that the most pressing and important problem facing the FDA from a public health point of view is the increasing cost and time involved in the approval of novel devices and the resulting unwillingness of investors, such as the VC community to finance these projects. The failure to develop new lifesaving or enhancing technology can produce as much harm to the public health as approving an unsafe technology.

In our opinion, a very small percentage of all applications, involving novel technology, are creating most of the challenges described in the task force report. Addressing this subset of applications would have a disproportionately positive effect on the operation of the Center as a whole.

The Science Council should have the authority, upon application of a sponsor, to designate an application as involving novel and important technology. Upon such a designation, the application would be entitled to collaborative review by both the Council and the appropriate Division. Important and novel issues raised by the application would be addressed at the earliest stages of review by this collaborative process. The Council would have very broad and flexible methods for involving external experts in the process on an extremely expedited basis. The council would also have the authority to consult, transparently to the sponsor, with other Divisions, if appropriate.

Most important, the process would involve reasonable access to the Directors of CDRH and ODE, who would be informed of major decisions by the Council and called upon to make high level public health policy judgments as appropriate. The goal of this collaborative process would be to expedite and routinize decision-making making by senior staff, rather than relying upon a disruptive 'appeal' process at the end of a drawn out disagreement between a Division and a Sponsor. Since the designation of an application as 'novel' will be entirely at the discretion of the Center, the Center will be able to manage resource allocation and test this process before deciding whether to commit substantial resources to it.

Bigesby, Michelle

From: Gadiock, Paul S
Sent: Tuesday, October 05, 2010 1:23 PM
To: Bigesby, Michelle
Subject: FW: NVCA Comments on CDRH 510(k) recommendations
Attachments: NVCA's Comments on CDRH's 510(k) recommendation Oct 2010 final.pdf

This attachment would replace (or be in addition to) FDA-2010-N-0348-0072. Thanks!

From: Desjardins, Philip R
Sent: Tuesday, October 05, 2010 12:23 PM
To: Gadiock, Paul S
Subject: FW: NVCA Comments on CDRH 510(k) recommendations

746.5734

Comment # 72

Philip R. Desjardins, JD
Policy Advisor
Office of the Center Director
Center for Devices and Radiological Health
Food and Drug Administration
(301) 796-5678
(240) 328-7174 (cell)
Philip.Desjardins@fda.hhs.gov

From: Shuren, Jeff
Sent: Tuesday, October 05, 2010 12:21 PM
To: Desjardins, Philip R
Subject: RE: NVCA Comments on CDRH 510(k) recommendations

I would ask Dockets how we can swap out the earlier comments and replace with the new set

Jeff

From: Desjardins, Philip R
Sent: Tuesday, October 05, 2010 12:20 PM
To: Shuren, Jeff
Subject: FW: NVCA Comments on CDRH 510(k) recommendations

NVCA submitted the wrong version of their comment and would like to replace it with the attached. Not sure how you want to handle the update but wanted you to have the most recent for the 1:00 with AdvaMed.

Philip R. Desjardins, JD
Policy Advisor

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Philip Desjardins@fda.hhs.gov

From: Sumi Singh [mailto:Sumi.Singh@nvca.org]
Sent: Tuesday, October 05, 2010 11:12 AM
To: Desjardins, Philip R
Cc: Kelly Slone
Subject: NVCA Comments on CDRH 510(k) recommendations

Hi Philip,
As a follow up to Kelly Slone's call to you yesterday, attached please find NVCA's comments.
Thanks,
Sumi

Sumi Singh
Public Policy Director
National Venture Capital Association
1655 North Fort Myer Drive, Suite 850
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August 27, 2010

Philip Desjardins
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave.
Building 66 Room 5447
Silver Spring, MD 20993-0002

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

Dear Mr. Desjardins,

On behalf of 60 medical device manufacturers and associated business members of the Indiana Medical Device Manufacturers Council (IMDMC), we respectfully request a 30-day extension of the comment period for the docket referenced above CDRH 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations.

Indiana is one of the world leaders in the medical device industry. In fact, according to the U.S. Census, Indiana is the 2nd largest state in the value of medical device products shipped. A wide variety of medical device manufacturers employ approximately 19,950 Hoosiers across the state, with a payroll of more than $1 billion ranking Indiana 7th in the nation in terms of medical device sector employment.

The IMDMC supports the efforts of FDA to assess and improve the 510(k) process. We welcome the opportunity to comment on the findings and recommendations documented in the CDRH Preliminary Internal Evaluations reports and are working to draft comments that we believe the CDRH will find helpful. Given the length of the reports and the numerous recommendations reflecting significant new requirements for many of our members, we are concerned that the published comment period does not allow adequate time to draft comments reflecting our members perspectives. Therefore, we request a 30-day extension to the comment deadline of October 4 to allow us the time needed to provide constructive feedback. Thank you for your consideration of our request.

Sincerely,

Danelle Miller
IMDMC President

Regulatory Counsel,
Roche Diagnostics Corporation

IMDMC Board Member Companies
Anson Group, Baker & Daniels, Bayer Diabetes Care, Biomet Inc., Cook Inc., DePuy Orthopaedics, Eli Lilly and Company, Hill Rom, Inc., Johnson & Johnson Inc., Medtronic Inc., Roche Diagnostics Corp., Zimmer Inc.

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October 4, 2010

Food and Drug Administration
Department of Health and Human Services
Washington, DC

Re: Center for Devices and Radiological Health Preliminary Internal Evaluations
Docket No. FDA-2010-N-0348

Dear Sirs:

Consumers Union, the independent, non-profit publisher of *Consumer Reports*[1] appreciates the opportunity to comment on Volumes I and II of the CDRH Preliminary Internal Evaluations as submitted by the Task Force on the Utilization of Science in Regulatory Decision Making and the 510(k) Working Group.

We strongly support the FDA's efforts to address problems that have plagued the device sector for a third of a century. We believe the Preliminary Reports' recommendations, if carried out, will help end the poor science and lax oversight that periodically results in patient deaths and injuries. Increased science and oversight is especially important because of the rapid increase in complex implants, due in part to aggressive advertising.

We offer a few specific comments:

MDUFA and Needed Resources

[1] Consumers Union of United States, Inc., publisher of Consumer Reports®, is a nonprofit membership organization chartered in 1936 to provide consumers with information, education, and counsel about goods, services, health and personal finance. Consumers Union's publications have a combined paid circulation of approximately 8.3 million. These publications regularly carry articles on Consumers Union's own product testing; on health, product safety, and marketplace economics; and on legislative, judicial, and regulatory actions that affect consumer welfare. Consumers Union's income is solely derived from the sale of Consumer Reports®, its other publications and services, fees, noncommercial contributions and grants. Consumers Union's publications and services carry no outside advertising and receive no commercial support.

We hope that you will incorporate the 2 Volume recommendations into your MDUFA resource renegotiation plans. Specifically, we support the key recommendation that

> "…CDRH take proactive steps to improve the quality of premarket data, particularly clinical data; address review workload challenges;[2] and develop better data sources, methods, and tools for collecting and analyzing meaningful post market information.

Since sufficient increased Congressional appropriations for staffing, scientific development, and post approval safety monitoring are unlikely given the government's unprecedented budget deficits, user fees should be increased to ensure FDA has the resources to enforce at least the same level of safety in devices as in pharmaceuticals (an area where we also believe more is needed).

On the specific issue of workload, before the industry and the FDA are rocked by serious safety scandals, MDUFA staffing increases should eliminate the need for the type of comment contained in the "staff feedback" where "other discussants noted challenges related to inflexible premarket review timeframes, with insufficient time allowed for review of complex systems."[3] We also recommend other tools to ensure that MDUFA fees do not distort the integrity of CDRH's decision-making.[4]

On the issue of quality of data, shocking are the reports of shoddy clinical trial submissions.[5] Is an implantable coronary device any less important than a pharmaceutical product? Apparently the quality of the applications is far inferior to those demanded by CDER—and we don't understand why they should be allowed at CDRH.

Incomplete Information

We urge you to begin immediately to revise FDA regulations 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." (emphasis added)

Those seeking approval of medical devices that will be used by potentially millions of patients over time should have a fiduciary-type duty to present all known studies, not just the favorable ones that promote their product or give only the sunniest of data. A device

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[2] As the Task Force notes (p. 36) "staffing increases have not kept pace with the growth in total premarket workloads." In addition, the excellent examples of differences in staff and management response to various questions and scenarios show that resources are needed for more cross-training. See also, the discussion on page 84-87 re the need for more training.

[3] Volume II: Task Force on the Utilization of Science in Regulatory Decision Making, p. 41.

[4] Testimony of Consumers Union before the FDA Listening Session on Generic Drug User Fees, September 17, 2010, Rockville, Maryland.

[5] Dhruva SS, et al., "Strength of Study Evidence Examined by the FDA in Premarket Approval of Cardiovascular Devices," JAMA, December 2009, Vol. 302, No. 24, pp. 2679-2685.

application should not be a game of "Find Waldo" where the FDA staff has to ferret out balanced or contradictory studies and data.[6]

The urgent need for UDI and Sentinel-type post-approval safety monitoring

We strongly support and urge you to strengthen the 510(k) working group recommendation that CDRH

> "…implement a unique device identification (UDI) and *consider*, as part of this effort, the *possibility* of using "real-world" data (e.g., anonymized data on device use and outcomes pooled from electronic health record systems) as part of a premarket submission for future 510(k)s"[7] (highlight added)

For many reasons, this should be done—not just 'considered' or a 'possibility'.

First, the UDI is grossly overdue and every day's delay threatens the lives and quality of care of patients with implants.

Second, once there is a UDI system, Sentinel-type data[8] should be routinely used to monitor outcomes—the durability and reliability and efficacy of key devices—and thus give consumers crucial comparative effectiveness information. People have a right to know how well an implanted medical device is likely to work in their bodies.

Third, being able to identify the quality of a product will help spur future innovation and quality. The industry should know that future 510(k) decisions will include data on the quality of the underlying product that the new application is related to and how that product compares to others in its sector. When the public can see this, they and their physicians will seek out higher quality products.

We realize that it will take several years for the UDI and Sentinel systems to become reality and be able to work together, but we urge you to begin planning now for the quality and safety revolution that these new systems can bring.

Post market Safety Studies

The Working Group discusses how often and why post market studies might be required (p. 78). As a Member of the IOM Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs, I recommend the Committee's *Letter Report* to the FDA in July, 2010, on this topic. http://www.iom.edu/Reports/2010/Ethical-Issues-in-Studying-the-Safety-of-Approved-Drugs-Letter-Report.aspx

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[6] See example in Volume I: 510(k) Working Group, p. 73.
[7] See also discussion in Volume I: 501(k) Working Group, p. 78.
[8] Established by FDAAA in 2007, Sentinel's goal is to have 100 million de-identified medical records available for analysis by July 1, 2012. The size of this database should enable very rapid identification of safety and efficacy problems that can be further researched.

Third Party Review

We believe that third party review is a public function and should be done by the FDA. The third party review system is subject to distortion and favoritism, and we urge stronger oversight and severely limiting any third party review of category II and III devices. The data provided in the Working Group report (pp. 93-94) raises very serious questions about the rationale for the third party review program and the quality of some outside reviewers' work product.

The need for non-conflicted experts

We urge that more attention be given to 'addressing issues of potential bias' in the proposal to

> "…develop a web-based network of external experts, using social media technology, in order to appropriately and efficiently leverage external expertise…."

We hope that any cadre of experts will also include conflict-of-interest-free individuals from the academic, consumer, and patient communities. The FDA is making strides in reducing the number of waivers in its Advisory Committee process—those gains should not be end-run my conflicted panels of industry-related experts consulted informally through 'social networks.'

We also urge you to consider a small grant program of assistance and support to non-profit, non-conflicted consumer or patient organizations (not ourselves, but others) to help prepare them for the difficult and complex task of providing pro-consumer/pro-patient advice in these sometimes very technical fields. Most small non-profits do not have the resources to pre-study every complex device question that may arise; they will often need assistance to be prepared to bring a non-financially-conflicted but scientifically sophisticated consumer perspective.

To help advance science and innovation, we especially support the Task Force's proposals for increased transparency and the sharing of review decisions and studies (e.g., Volume II, p. 37). All guidances should be made public. For example, the language on page 35 of the Task Force report (Volume II) says "in these letters, *some* of which have been made available to the public on the Center's website" (emphasis added). Again, all such guidances and letters should be public record.

Least Burdensome should not mean Poor Quality

We thank you for your discussion of 'least burdensome' and for pointing out that this phrase must be fully balanced with protecting the public health. It probably is no burden to make a shoddy or dangerous or ineffective product—but it is the job of the FDA to protect patients against this type of abuse.

Labeling and patient information

In the discussion on labeling, we strongly support a single, on-line source of all labels (although it should be clear that such labeling does not alter, in any way, an individual's rights in court and does not pre-empt any legal actions). But the FDA should do more to make information about the efficacy and safety of devices simple and easy for patients to use. In the pharmaceutical sector, the FDA is at long-last moving to a single document, which we hope will stress some quantitative information about the drug's safety and efficacy, ideally in comparison to other similar medicines. We urge the FDA to develop a similar labeling program for devices. Consumers constantly seek information on auto quality, safety, and mileage efficiency. Certainly a patient getting a hip replacement deserves the latest data on durability and safety—and the miles you can walk before it wears out!

Thank you for your consideration of these views.

Sincerely,

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AdvaMed
Advanced Medical Technology Association

September 21, 2010

Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane, Room 1061
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Docket No. FDA-2010-N-0348: "Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations"

Dear Sir/Madam:

On behalf of AdvaMed, the Advanced Medical Technology Association, I am pleased to resubmit our enclosed proposal for strengthening the 510(k) process by identifying a small, focused subset of Class II devices that may require additional information to support a substantial equivalence determination. AdvaMed originally sent this proposal directly to Dr. Jeffrey Shuren on May 12, 2010. The proposal was subsequently discussed in a meeting with Drs. Hamburg, Shuren, other FDA representatives and AdvaMed representatives on May 21, 2010.

AdvaMed represents manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatments. AdvaMed member companies produce the medical devices, diagnostic products and health information systems that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed members range from the largest to the smallest medical technology innovators and companies.

AdvaMed is resubmitting the enclosed proposal to clarify our position and to distinguish it from CDRH's proposal as it relates to the specific recommendations in the 510(k) Working Group report to create a "Class IIb" subset of 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."[1] As discussed in more detail below and in the enclosed proposal, AdvaMed contemplated a limited, focused subset of Class II

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[1] Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations. August 2010. Page 76. Available at: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM220784.pdf.

devices that would be subject to enhanced pre- and postmarket requirements. FDA public comments, however, suggest that a more expansive set of device types would be included in this new "Class IIb" with broader pre- and postmarket requirements not contemplated by the AdvaMed proposal. Please note that AdvaMed also will be submitting extensive, detailed comments on the two CDRH reports to the docket referenced above, but wished to enter AdvaMed's position related to a small focused subset of Class II devices into this docket at this time, as it differs from CDRH's recommendation for a new product classification.

AdvaMed's enclosed proposal includes recommendations that FDA establish requirements for additional information for a ***small, focused subset*** of Class II medical devices for which enhanced information requirements are necessary to adequately evaluate the substantial equivalence of the device. The information could include clinical data summaries of published and/or unpublished reports on the subject device and/or on other clinical experience of either the device in question or a justifiably comparable device (when animal and bench testing are not sufficient to provide an adequate characterization of the device) and other device-specific requirements that would not be applicable to the entire subset. The subset list would be published in the Federal Register for public comment. AdvaMed's proposal did not contemplate and does not agree with the creation of a new class of medical devices (i.e., "Class IIb," as recommended by CDRH). Further, as noted above, we are aware of FDA public comments suggesting that a more expansive set of devices would be included in this new "Class IIb." Such a new risk-based device classification necessitates revision of the Food, Drug and Cosmetic Act (the Act), which requires a statutory change.

AdvaMed's proposal addresses a small, focused subset of devices that would be subject to additional submission requirements. The types of devices that would fall into this subset would be determined based on risk management processes, and could include permanent implants, life-sustaining devices, and life-supporting devices where the potential for increased concern exists such that special requirements are appropriate to assure the safety and effectiveness of these devices and to clarify data expectations for manufacturers seeking clearance for devices in these classes. As more experience is gained and the use of each device becomes well-established with a historical track record of safe and effective use, the device would be removed from the subset. Thus, AdvaMed's proposal effectively establishes a sub-tier of regulation for a limited and dynamic subset of devices subject to 510(k) clearance. Under the proposal, FDA would identify device types subject to the enhanced information requirements and publish the list in the Federal Register for comment. Importantly, the AdvaMed proposal can be accomplished without necessitating a statutory change.

Thank you for the opportunity to enter AdvaMed's proposal into the public docket.

Respectfully submitted,

Janet Trunzo
Executive Vice President
Technology and Regulatory Affairs

Enclosures

Proposal for Strengthening the 510(k) Process for a Subset of Medical Devices

The Premarket Notification 510(k) regulatory pathway ensures that diverse medical devices are appropriately regulated by creating a risk-based, science-driven classification system that *includes a comprehensive and vigorous review of device performance and test data.* A 510(k) submission for even simple devices may contain hundreds and in some cases thousands of pages of evidence demonstrating the safety and effectiveness of the device under review, including, where appropriate, clinical testing and data. By permitting incremental device improvements, today's 510(k) regulatory process is a successful and effective means to ensure the safety and effectiveness of medical technology while encouraging device development and facilitating the availability of high quality medical devices to meet the needs of the American public. Every year, approximately 3,600 new and improved devices are cleared via the 510(k) process—a remarkable record of achieving the twin goals of supporting medical innovation and providing the regulatory rigor necessary to assure that devices are safe and effective.

Challenges

Over the past two years, concerns have been raised regarding the adequacy of the 510(k) process to assure the safety and effectiveness of certain products that are cleared through the 510(k) regulatory pathway. AdvaMed believes much of this concern may arise from a lack of understanding among some stakeholders about the requirements of the 510(k) process and how it fits within the broader regulatory scheme including establishment registration and medical device listing, medical device reporting, good manufacturing practices as demonstrated by compliance with the quality system regulation, labeling requirements and provisions against adulteration and misbranding. This broad regulatory scheme assures that there is adequate FDA oversight and control throughout the medical device life-cycle.

FDA has also raised concerns, specifically regarding:

- The need for clinical information for some products when bench or animal testing are not adequate to provide assurance of safety and effectiveness or does not provide adequate understanding of the device
- The lack of access to final labeling copy prior to market introduction
- The lack of visibility to device changes that take place after marketing clearance including labeling and design changes that do not meet the criteria for a new 510(k) submission and
- The limits of postmarket controls.

More broadly, FDA has raised concerns about key aspects of reliance on predicates to determine the safety and effectiveness of new devices. For example, FDA has asked whether it is appropriate to clear a device based on the use of older predicates that no longer represent the standard of care and has raised concerns about the use of multiple or split predicates.

Current State

For the majority of Class II devices with low and moderate risk, or whose technical and clinical performance is well characterized, the current premarket notification requirements are adequate and appropriate, and provide FDA with the necessary information to conduct its substantial equivalence review.

For other devices whose intended use has the potential for increased concern or whose technology is being used in a new application, FDA has the authority to request any data necessary to assure the product is safe and effective. FDA also has the authority to require special controls. Special controls are information specific to a particular device type beyond the basic requirement of substantial equivalence that is considered important in the review of a device. Special controls can be applied to both the data that needs to be submitted for a device to be cleared for marketing beyond the basic requirement of substantial equivalence and to requirements relating to conditions of use. Special control documents have been developed for devices such as contact lenses, influenza assays, IV sets, sutures, and diagnostic ultrasound devices and transducers.

The 510(k) system works well for most devices, but in more complex submissions there appears to be a lack of clarity and consistency in the 510(k) review process. While there is no evidence to support that this has resulted in the clearance of unsafe or ineffective products, it has been a source of frustration and delay for manufacturers, especially new and small entities, trying to provide appropriate evidence to meet FDA requirements and has contributed to public concern about the process.

PROPOSAL

To meet FDA's mission of both protecting the public health *and* advancing the public health by speeding innovations that make devices safer and more effective, and to maintain the integrity of the 510(k) program, we recommend FDA establish requirements for additional information for a subset of Class II medical devices and *in vitro* diagnostics. Under the proposal, FDA would identify the device types subject to the enhanced information requirements and publish the list of affected device types in the Federal Register for public comment.

The list of device types to which the additional requirements apply would be reviewed periodically to add new device types where appropriate. Similarly, as more experience is gained and the use of a device becomes well-established with a historical track record of safe and effective use, the device would be removed from the list

Criteria for Identification of Class II Device Subset

The following criteria are recommended for determining which Class II devices should fall into a subset that would be subject to additional submission requirements. These criteria identify devices that may present a higher level of concern associated with their intended use or with their use of technology in a new application. These devices clearly meet the requirements for Class II designation and do not meet the requirements for Class III.

Device types that may fall into this Class II subset could be the following:

- Permanent implants
- Life-sustaining
- Life-supporting

However, not all device types that are permanent implants, life sustaining, or life supporting would be subject to the additional submission requirements as many of these device types have a long history of safe and effective use and do not present added concern with their intended use. FDA would determine the subset of this group for which additional requirements are appropriate *based on risk management processes*. At a minimum, if the device type meets the following criteria, additional requirements would not be necessary:

- Well-characterized uses
- Well-characterized technologies
- A record of safety in clinical use or
- Up-to-date standards, guidance and/or special controls that have proven effective.

Some examples of these devices would be sutures and dental implants.

Enhanced Submission Requirements for the Class II Device Subset
510(k) submissions for Class II devices subject to the enhanced information requirements would include the following information:

- **Technical and Clinical Information Summary**
  - Technical Information
    Although bench testing and animal summary data are typically provided in a 510(k) submission, device specific testing may be appropriate for an identified device type (see Device-Specific Requirements *below*).

  - Clinical Information
    When animal and bench testing are not sufficient to provide an adequate characterization of the device, a summary of clinical information is provided. This includes relevant information about clinical experience with the device as well as experience with similar devices and the predicate device(s). Sources of clinical information may include:
    - Published and/or unpublished reports on other clinical experience of either the device in question or a justifiably comparable device
    - Results of pre- and postmarket clinical investigation(s) or other studies reported in the scientific literature of a justifiably comparable device
    - Results of pre- and postmarket clinical investigation(s) of the device

- **Labeling Elements** – Standard label information include indications for use, warnings and precautions and contra-indications.

Device-Specific Requirements – These device-specific requirements that FDA may require at its discretion for identified device types within this subset are in addition to the general enhanced submission requirements. These could include:

- Specification of additional evidence required to demonstrate safety and effectiveness, conformance to recognized standards, or other requirements related to the device types and

- A summary of manufacturing and controls information in the form of a flow chart or other simple means to establish baseline information to which subsequent 510(k) submissions and post-clearance periodic reports could be compared.

Instructions for Use at Time of Market Introduction for this Subset
Manufacturers of Class II devices subject to the enhanced information requirements would also be required to submit a copy of the device's final Instructions for Use at the time of first marketing of the device.

Post-clearance Periodic Reports for this Subset
Propose a system, that on a case by case basis, enables FDA to request at clearance, periodic reports for visibility to important changes to 510(k) baseline information and post-clearance experience after a device is marketed. Manufacturers of Class II devices subject to the enhanced information requirements *could* also provide to FDA Periodic Reports on marketed products every three years after the date of clearance that *could* include the information such as the following:

- **Design changes** [that do not meet the criteria for submission of a new 510(k)]
- **Labeling changes** [that do not meet the criteria for submission of a new 510(k)]
- **Summary of post-clearance experience** (e.g., MDRs; complaints; clinical information published within the reporting period) and
- **Update to the applicable device-specific requirements**

AdvaMed Proposal Responds to FDA concerns and Improves the Process
The current three-tiered classification structure of FDA device and diagnostic regulation is a risk-based approach. As such, it represents a practical and effective system for regulating an industry that is both very innovative and very diverse. The proposal effectively establishes a sub-tier of regulation for a limited subset of devices subject to 510(k), which could be accomplished without necessitating a statutory change. The additional requirements for this sub-tier add both transparency and consistency to the process for FDA and manufacturers while at the same time using the existing risk-based structure to increase the level of evidence associated with a targeted set of device types.

For the relevant subset of devices, this proposal assures that FDA has adequate clinical information needed when it makes clearance decisions, and allows FDA to specify in advance what additional information is necessary and appropriate to demonstrate safety and effectiveness. It assures that FDA has a copy of final labeling at time of market introduction, provides visibility for device and labeling changes that take place after market clearance, and provides FDA with additional postmarket data without burdening FDA with unnecessary documents or data.

With regard to concerns that reliance on predicates may not provide assurance of safety and effectiveness for some devices, the proposal addresses this issue directly by

establishing specific evidence requirements for those categories of devices[1] where such requirements are necessary. Issues regarding use of outdated predicates, predicate "creep," and use of multiple or split predicates all become irrelevant if there are specific evidentiary requirements that must be met regardless of the relationship of the new product to a predicate. As we have noted in AdvaMed's comments to the 510(k) review process docket, AdvaMed does not believe that FDA is required to clear any product based on any predicate without data providing satisfactory assurance to FDA that the new product is safe and effective. But the use of additional submission requirements (special controls) would clarify the evidence that manufacturers need to submit to gain product clearance, provide greater consistency in decision-making, and improve public confidence in FDA's decisions.

[1] To be clear, all 510(k) submissions include comprehensive information on the testing and performance of the device under review.

Kathryn Branca
SCC Soft Computer
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September 22nd, 2010

Division of Dockets Management (HFA–305)
Food and Drug Administration
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RE: Docket No. FDA-2010-N-0348

In response to the August 5th, 2010, Federal Register request for comments on the 510(k) Working Group Preliminary Report and Recommendations, SCC Soft Computer would like to submit the following:

SCC Soft Computer supports the recommendation in section 5.1.1.1, page 45, of Volume I, that the intended use and indications for use be consolidated into a single term, with guidance provided by the Center as to how this would affect the inclusion of required indications for use within 510(k) submissions. SCC Soft Computer is also in agreement that further clarification is needed regarding what is considered an actual change in intended use based on the addition of different technological characteristics.

SCC Soft Computer is in agreement that specific devices should not be used as a predicate because of safety and effectiveness concerns as described in section 5.1.2.1, page 57, of Volume I. Guidance should be provided by the Center describing how a medical device manufacturer would know that a specific device should not be used as a predicate.

As a manufacturer of medical device software, SCC Soft Computer is in agreement that the existing guidance pertaining to modifications requiring a new 510(k) needs to be revised, as mentioned in section 5.2.1.1, page 69, of Volume I. Specifically, the revised guidance should elaborate on how modifications to medical device software will warrant a new 510(k) submission, including whether the decision is based on the number of individual change versus the types of modifications. The guidance should also explain the types of modifications that are eligible for a Special 510(k) submission.

SCC Soft Computer feels that clarification is needed in section 5.2.1.1, page 69, of Volume I, to clearly define what types of device modifications would need to be included in the periodic updates to the Center. A mechanism to provide these updates, in an electronic format, would need to be supplied. The "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)" guidance would need to be revised to clearly explain the approach a medical device manufacturer should use when evaluating modifications to determine if a 510(k) is warranted.

SCC Soft Computer has several concerns regarding the proposal of providing additional labeling to the agency after a device has obtained its 510(k) clearance, as described in section 5.2.2.2, page 86, of Volume I, due to the amount of information that would be required to send. Prior to implementation of this proposal, we suggest that a method for electronic submission of labeling be clearly defined and communicated to the industry. We also feel that the Center needs to describe how these labeling updates will be used. Will the Center be comparing them to the originally submitted labeling or will they be used for another purpose? Finally, we do not feel that annual submission of labeling updates, as part of establishment registration, is necessary, especially if the submission of device modifications mentioned above takes place.

SCC Soft Computer looks forward to continued improvements of the 510(k) program.

Sincerely,

Kathryn L Branca

Kathryn Branca
Director of Quality Management
SCC Soft Computer

September 28, 2010

Division of Dockets Management (HFA-305)
Food & Drug Administration
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Rockville, MD 20852.

Re: Docket # FDA-2010-N-0348
Preliminary Reports & Recommendations from:
510(k) Working Group
Task Force on the Utilization of Science in Regulatory Decision Making

Dear FDA,

This letter represents the views of RTI Biologics, Inc. (RTIB) concerning the recommendations of the 510(k) Working Group and the Task Force on the Utilization of Science in Regulatory Decision Making. RTIB is the leading provider of sterile biological implants for surgeries around the world with a commitment to advancing science, safety and innovation. RTIB prepares human donated tissue and bovine tissue for use in orthopedic, dental, hernia and other specialty surgeries. We appreciate the opportunity to respond to FDA's recent internal evaluations.

RTIB believes a 510(k) system does not require statutory changes in order to facilitate the availability of important treatment options for American patients and physicians. The preliminary report by FDA's 510(k) Working Group's report expresses many valid concerns about the premarket review process, however, these concerns could be addressed by improving supporting processes, such as the reviewer training program and mechanisms by which special controls, consensus standards and guidance are established.

Because these two reports are based on FDA internal evaluations, we suggest that no changes be implemented until the Institute of Medicine report on the 510(k) process (expected early 2011) is published and stakeholders are given an opportunity to respond. Once all input is considered and FDA determines a course of action, stakeholders should also be afforded the opportunity to provide feedback on the details of each initiative.

We appreciate the opportunity to comment on these two important initiatives. More detailed comments on the individual proposals are provided in the attached chart.

Respectfully Submitted,

Lisa Simpson
Director, Regulatory Affairs
RTI Biologics, Inc.

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Section	Topic *Implementation*	510(k) Process Proposal	RTIB Response
5.1.1.1	**Same Intended Use** Lack of a Clear Distinction between terms *Guidance*	CDRH should 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.	We disagree with the proposal to consolidate the two concepts. Because intended use and indications for use are distinctly different concepts, we do not see a benefit in consolidating the terminology. We believe this approach would only perpetuate the confusion. Instead, we recommend that better guidance concerning how the current terms relate to the 510(k) regulatory framework be provided. Furthermore, we suggest that device-specific guidance may be needed in some circumstances. If certain device types are particularly problematic with respect to differentiation of the two concepts, FDA should provide additional guidance to industry and reviewers. FDA should also ensure that ODE staff training programs are properly aligned with both the conceptual interpretation and the device-specific issues in their areas of responsibility.
5.1.1.1	**Insufficient Guidance for 510(k) Staff and Industry** *Guidance*	CDRH should clearly identify the characteristics that should be included in the concept of intended use.	

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Section	Topic *Implementation*	510(k) Process Proposal	RTIB Response
5.1.1.1	**Off-Label Use** *Statutory*	CDRH should explore pursuing a statutory amendment to section 513(i)(1)(E) of the Federal Food, Drug and Cosmetic Act to provide FDA with express authority to consider an off-label use, in certain limited circumstances, when determining the "intended use" of the device under review through the 510(k) process	We do not agree that FDA should have the authority to consider uses that are outside the proposed labeling submitted by the device manufacturer. This practice could create an unreasonable regulatory burden for manufacturers, particularly in cases where the off-label use corresponds to a higher device class. FDA already has a mechanism for clearance of devices as "substantially equivalent with limitations". We do not believe it is appropriate for FDA to place additional constraints on manufacturers in an attempt to solve a problem that is rooted in the practice of medicine. FDA should consider creating a better communication mechanism whereby clinicians are informed of the hazards of off-label uses.
5.1.1.2	**Different Questions of Safety and Effectiveness** Inconsistent Terminology *Guidance*	CDRH should reconcile the language in its 510(k) flowchart with the language in section 513(i) of the Food, Drug and Cosmetic Act including "different technical characteristics" and "different questions of safety and effectiveness."	We support clarification of these terms through revision of existing guidance and the additional training to increase consistency between reviewers and across managers.
5.1.1.2	**Insufficient Guidance for 510(k) Staff and Industry** *Guidance/ Training*	CDRH should revise existing guidance to provide clear criteria for identifying "different questions of safety and effectiveness"	
5.1.1.2		CDRH should develop and provide training for reviewers and managers on how to determine whether a 510(k) raises "different questions of safety and effectiveness"	

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Section	Topic *Implementation*	510(k) Process Proposal	RTIB Response
5.1.2.1	**Concerns about Predicate Quality** *Guidance*	CDRH should consider developing guidance on when a device should no longer be available for use as a predicate because of safety and/or effectiveness concerns.	We generally support the development of guidance on the selection and use of predicates. We agree that allowing an unsafe or ineffective predicate to persist within the system is not in the best interest of public health. However, a predicate elimination policy should have very specific criteria, such as submission fraud or design flaws that have been associated with safety or effectiveness issues. For example, if a predicate device were determined to be unsafe or ineffective because it was not manufactured in accordance with the cleared design and there is no compelling reason to believe the design itself is flawed, it should not necessarily be eliminated as a predicate. A corresponding policy for products already cleared using cancelled predicates would also need to be defined. Also, due to the cost of improving technology, CDRH needs to be careful not to reject a predicate simply because the technology has evolved and improved. Any requirement for a manufacturer to re-establish safety and effectiveness of a device because of improved technology would hinder innovation.

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Section	Topic *Implementation*	510(k) Process Proposal	RTIB Response
5.1.2.2	**Rescission Authority** *Regulatory Change*	CDRH should consider issuing a regulation to define scope, grounds and appropriate procedures for exercise of its authority to fully or partially rescind a 510(k) clearance	We agree with this initiative.
5.1.2.3	**Use of "split" and "multiple" predicates** *Guidance/ Training*	CDRH should develop guidance on appropriate use of more than one predicate, explaining when "multiple predicates" may be used.	We agree that FDA should continue to permit use of multiple predicates. We also agree that use of split predicates is a valid concern; however, we do not believe it is necessary to eliminate the practice. If manufacturers were required to provide a comparative risk analysis and robust design validation information in support of their use of split predicates, FDA would be better equipped to decide whether the device is substantially equivalent. We encourage FDA to issue guidance concerning the proper use of predicates and ensure that reviewers are trained so that uniform practices are applied.
5.1.2.3		CDRH should explore possibility of explicitly disallowing the use of split predicates. CDRH should update its existing bundling guidance to clarify the distinction between multi-parameter or multiplex devices and bundled submissions.	
5.1.2.3		CDRH should analyze the apparent association between 5 or more predicates and adverse events. CDRH should provide training for reviewers and managers on reviewing 510(k)s that use multiple predicates	
5.1.3	**De novo** *Guidance*	CDRH should revise existing guidance to streamline the current implementation of the de novo classification process and clarify its evidentiary expectations for de novo requests. CDRH should consider exploring the possibility of establishing a generic set of controls for devices classified into Class II through the de novo process, and which could be augmented with additional device-specific special controls as needed.	In cases where a suitable device predicate does not exist, the manufacturer should be able to submit the De Novo application initially, as opposed to submitting a traditional 510(k), only to have an NSE decision rendered. There should be some other mechanism whereby the manufacturer and FDA can agree that the De Novo route is the best option prior to submission.

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Section	Topic *Implementation*	510(k) Process Proposal	RTIB Response
5.2.1.1	**Unsupported Device Modifications** *Guidance*	CDRH should 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)	We support revising existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k), including which are eligible for Special 510(k).
5.2.1.1		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).	Annual updates should be sufficient. If this requirement is implemented, FDA should establish a fair policy for resolving differences of opinion with the manufacturer. In other words, if FDA disagrees with the manufacturer s letter-to-file and believes a 510(k) is needed, there should be a clear policy on how to handle modified products already on the market. CDRH should not charge user fees for their review of these periodic updates.
5.2.1.2	**Quality of Submissions** *Guidance*	Lack of Clarity. The Center should develop guidance on how submitters should develop and use an assurance case to make adequate, structured, and well-supported predicate comparisons in their 510(k)s.	We support development of a guidance concerning expectations for predicate comparisons in 510(k)s. CDRH should ensure that the guidance is not overly prescriptive and does not increase the data requirements to support changes. We recommend that CDRH establish mechanisms to ensure expectations remain consistent between reviewers and industry.

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Section	Topic *Implementation*	510(k) Process Proposal	RTIB Response
5.2.1.2	**Photos, schematics** *Guidance*	CDRH should explore the possibility of requiring each 510(k) submitter to provide as part of its 510(k) detailed photographs and schematics of the device under review, in order allow review staff to develop a better understanding of the device s key features. CDRH should also explore the possibility of requiring each 510(k) submitter to keep at least one unit of the device under review available for CDRH to access upon request, so that review staff could, as needed, examine the device hands on as part of the review of the device itself, or during future reviews in which the device in question is cited as a predicate.	We do not support a requirement to provide photographs and schematics as part of a submission. Manufacturers should have the option to provide visual data to support review of their 510(k) s but should not be required to provide data, photographs or schematics to support a competitor s submission. We also do not support the suggestion that CDRH require the submitter to keep samples of 510(k) cleared devices. This requirement would be burdensome for manufacturers.
5.2.1.2	**Improper use of recognized standards** *Guidance*	CDRH should provide additional guidance and training for submitters and review staff regarding the appropriate use of consensus standards, including proper documentation within a 510(k). CDRH should also consider revising the requirements for declarations of conformity with a standard, for example by requiring submitters to provide a summary of testing to demonstrate conformity if they choose to make use of a declaration of conformity.	We agree that additional guidance and training will facilitate the review process when consensus standards are cited in a 510(k); however, there are many device types for which FDA recognized consensus standards do not exist. Therefore, we also suggest that FDA accelerate programs by which consensus standards are adopted.

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Section	Topic *Implementation*	510(k) Process Proposal	RTIB Response
5.2.1.2	**Incomplete Information** *Regulatory Change*	The 510(k) Working Group recommends that CDRH consider revising 21 CFR 807.87, to explicitly require 510(k) submitters to provide a list and brief description of all scientific information regarding the safety and/or effectiveness of a new device known to or that should be reasonably known to the submitter. The Center could then focus on the listed scientific information that would assist it in resolving particular issues relevant to the 510(k) review.	This information should only be required if there are outstanding safety and/or effectiveness questions that have not been answered through the use of special controls, consensus standards or requirements stated in FDA device-specific guidance. A blanket requirement to provide the information up front, for all categories of 510(k) devices would be overly burdensome. Manufacturers often collect this type of information as part of their product development processes; however, it should be optional, not mandatory for certain 510(k) submissions. If a manufacturer submits a Special 510(k), for example, this level of literature support would not typically be collected and should not be required by FDA. This requirement may not be value-added for some devices.

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Section	Topic *Implementation*	510(k) Process Proposal	RTIB Response
5.2.1.3	**Type and level of Evidence Needed** *Guidance*	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.	The proposed class IIb subset, as described, is not a change to the statutory device classification system or the 510(k) statutory framework. FDA should therefore ensure this proposal remains an administrative distinction and does not evolve into a new regulatory system or device class. Related policies should have a corresponding measure of flexibility. For example, it should not take a great amount of effort or time for FDA to move a device from Class IIb to Class IIa as the safety and effectiveness profile becomes more established. FDA should also establish a mechanism by which stakeholders can propose moving a device from Class IIb to Class IIa.
5.2.1.3	**Clinical Information** *Guidance*	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".	FDA already has the authority to call for clinical data when preclinical testing is not sufficient to support substantial equivalence to a predicate device. It would be helpful for FDA to give manufacturers more visibility to the decision-making process in this regard. We agree it is important for FDA to define clinical data since the term has yet to be officially defined by regulation or policy. We recommend that the Global Harmonization Task Force definition be adopted. This definition allows use of studies reported in the scientific literature, as well as published and/or unpublished reports of clinical experience from either the device in question or a justifiably comparable device.

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Section	Topic *Implementation*	510(k) Process Proposal	RTIB Response
5.2.1.3	**Postmarket Information** *Regulatory/ Guidance*	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. CDRH should continue its ongoing effort to implement a unique device identification (UDI) system and consider, as part of this effort, the possibility of using real-world data (e.g., anonymized data on device use and outcomes pooled from electronic health record systems) as part of a premarket submission for future 510(k)s.	Post-market studies should not be required for 510(k) products as this could prove to be overly burdensome to industry. If FDA has determined that a new device is substantially equivalent to a predicate, it is unclear why the new device might require a post-market study while the predicates (cleared under the former system) do not. We agree that FDA guidance is needed if post-market authorities are expanded. If FDA chooses to implement post-market study requirements, this data should also be used to lessen regulatory burden (e.g. move devices from the class IIb to the Class IIa category) in an expedient manner. FDA should ensure that UDI requirements harmonize with global unique device identifier initiatives.
5.2.1.3	**Manufacturing Process Information** *Guidance*	CDRH should 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.	Manufacturing processes are often not fully implemented at the time of 510(k) submission; therefore, manufacturing process information should not be required.

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Section	Topic *Implementation*	510(k) Process Proposal	RTIB Response
5.2.1.3		CDRH should clarify when it is appropriate to use its authority to withhold clearance on the basis of a failure to comply with good manufacturing 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	Inspections should not be required as a condition of clearance for 510(k) devices. This will place unnecessary burden on industry, particularly because FDA is not currently resourced to conduct such inspections in a timely manner. We recommend that FDA concentrate efforts and resources on increasing the inspection frequency of class IIb manufacturers instead of requiring a pre-clearance inspection.
5.2.2.1	**Product Codes** *Guidance*	CDRH should develop guidance and Standard Operating Procedures on the development and assignment of product codes.	We support guidance and SOPs for the development and assignment of product codes. We believe further definition of and guidance on the product code development process will be beneficial to both FDA staff and industry.
5.2.2.2	**510(k) Databases** **Limited tools for Review Staff and Outside Parties** *Guidance*	CDRH should develop a database that includes, for each cleared device, a verified 510(k) summary, photographs and schematics of the device.	We are generally in favor of a database with verified 510(k) summaries. However, provision of photographs, schematics etc. should be left to the discretion of the manufacturer as this presents concerns for intellectual property. Posting drawings or detailed specifications would be extremely detrimental to manufacturers as it provides competitors an advantage.
5.2.2.2	**510(k) summaries** *Guidance*	CDRH should 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.	We are in favor of guidance and SOPs to support consistency in 510(k) summary information, including a standardized electronic template. We believe access to more complete 510(k) summaries benefits the public, industry and FDA.

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Section	Topic *Implementation*	510(k) Process Proposal	RTIB Response
5.2.2.2	**Lack of Ready Access to Final Device Labeling** *Regulatory Change*	CDRH should revise existing regulations to clarify the statutory listing requirements for the submission of labeling. CDRH should also explore the feasibility of requiring manufacturers to electronically submit final device labeling to FDA by the time of clearance or within a reasonable period of time after clearance, and also to provide regular, periodic updates to device labeling, potentially as part of annual registration and listing or through another structured electronic collection mechanism. 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.	We are generally supportive of CDRH requiring manufacturers to electronically submit final device labeling to FDA within a reasonable time period after clearance. However, with regards to periodic updates to device labeling, this should be required no more than once a year as more frequent updating would be unreasonably burdensome to device manufacturers. Further, updated labeling should not be required until FDA establishes the electronic system. If FDA intends on posting "final device labeling" or "preliminary labeling" on the public 510(k) database, we recommend a disclaimer be added that clarifies medical device users should refer to the labeling accompanying the product for the most up-to-date labeling. We believe it could be detrimental to the public health if device labeling from a source other than the labeling accompanying the product is utilized in medical device application.
5.2.2.2	**Limited Information on Current 510(k) Ownership** *Guidance/ Regulatory Change*	CDRH should develop guidance and regulations regarding appropriate documentation of transfers of 510(k) ownership.	We agree with the proposal to develop guidance and regulation involving 510(k) ownership transfer.
5.3.1.1	**Training** *Training/ Knowledge-Sharing*	CDRH should enhance training, professional development, and knowledge-sharing among reviewers and managers, in order to support consistent, high-quality 510(k) reviews CDRH should consider establishing a Center Science Council to serve as a cross-cutting oversight body that can facilitate knowledge-sharing across review branches, divisions, and offices.	We support CDRH efforts to enhance staff training and professional development.

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Section	Topic *Implementation*	510(k) Process Proposal	RTIB Response
5.3.1.2	**Third-Party Review** *Guidance/ Training*	CDRH should develop a process for regularly evaluating the list of device types eligible for third-party review and adding or removing device types as appropriate based on available information. The Center should consider, for example, limiting eligibility to those device types for which device- specific guidance exists, or making ineligible selected device types with a history of design-related problems.	We support the proposal to regularly evaluate device types eligible for third-party review, including development of a mechanism to share more information with the third-party reviewers. There should be a mechanism to remove proprietary information prior to sharing information with third-party reviewers. We agree it is important to align the training programs for in-house and third-party reviewer programs.
5.3.1.2		CDRH should enhance its third-party reviewer training program and consider options for sharing more information about previous decisions with third-party reviewers, in order to assure greater consistency between in-house and third-party reviews	
5.3.2	**Metrics** *Legislative (MDUFMA amendments) Internal FDA metrics*	CDRH should develop metrics to continuously assess the quality, consistency, and effectiveness of the 510(k) program, and also to measure the effect of any actions taken to improve the program. As part of this effort, the Center should consider how to make optimal use of existing internal data sources to help evaluate 510(k) program performance.	We support this initiative.
5.3.2		CDRH should periodically audit 510(k) review decisions to assess adequacy, accuracy, and consistency. The ongoing implementation of iReview (described in Section 5.3.2 of this report), as part of the Center's FY 2010 Strategic Priorities, could assist with this effort by allowing CDRH to more efficiently search and analyze completed reviews. These audits should be overseen by the new Center Science Council, described above, which would also oversee the communication of lessons learned to review staff, as well as potential follow-up action	

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Section	Topic *Implementation*	Task Force on the Utilization of Science in Regulatory Decision Making Proposal	RTIB Response
4.1.1.1	**Premarket Review** *Guidance*	**Interpretation of the "Least Burdensome" Provisions** CDRH should revise its 2002 "least burdensome" guidance to clarify the Center's interpretation of the "least burdensome" provisions of the Federal Food, Drug, and Cosmetic Act (21 USC §360c(a)(3)(D)(ii) and 21 USC §360c(i)(1)(D.	We support this initiative.
4.1.1.1	**Quality of Clinical Data** *Guidance*	CDRH should 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 also continue to engage in the development of domestic and international consensus standards, which, when recognized by FDA, could help establish basic guidelines for clinical trial design, performance, and reporting. In addition, CDRH should consider expanding its ongoing efforts related to clinical trials that support PMAs, to include clinical trials that support 510(k)s.	We are in favor of the CDRH improving upon the quality of clinical trials by developing guidance on the design of clinical trials used to support premarket submissions. We believe establishing an internal team of clinical trials experts for advising other CDRH staff, as well as prospective IDE applicants or those seeking feedback through a pre-IDE meeting process, would be extremely beneficial. We also support development of domestic and international consensus standards related to clinical trials.

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Section	Topic *Implementation*	Task Force on the Utilization of Science in Regulatory Decision Making Proposal	RTIB Response
4.1.1.1	*Guidance*	CDRH should work to better characterize the root causes of existing challenges and trends in IDE decision making, including evaluating the quality of its pre-submission interactions with industry and taking steps to enhance these Interactions as necessary.	We are in favor of FDA evaluating the current state of premarket interactions with industry in order to improve upon these interactions. Further, we believe developing supplemental guidance on pre-IDE meetings will assist in enhancing the overall quality of these types of interactions.
4.1.1.1	**Review Workload** *Internal FDA procedures*	CDRH should consider creating a standardized mechanism whereby review Offices could rapidly assemble an ad hoc team of experienced review staff from multiple divisions to temporarily assist with time-critical work in a particular product area, as needed, in order to accommodate unexpected surges in workload.	We believe that ad hoc teams of experienced reviewers could be used to accommodate workload surges. The reviewer training programs should account for the ad hoc teams to ensure they remain competent in their areas of special assignment. We agree with the Task Force in that such an approach would not be an appropriate solution for long term.
4.1.1.1		CDRH should assess and better characterize the major sources of challenge for Center staff in reviewing IDEs within the mandatory 30-day timeframe, and work to develop ways to mitigate identified challenges under the Center s existing authorities.	
4.1.1.2	**Postmarket Oversight** *Guidance/Internal FDA procedures*	CDRH should continue ongoing efforts to develop better data sources, methods, and tools for collecting and analyzing meaningful postmarket information, consistent with the Center s FY 2010 Strategic Priorities.	We support expanding upon existing methods and tools for gathering post-market surveillance data. We believe these efforts should be in sync with other national and international efforts.
4.1.2	**Staffing levels, training and knowledge management** *Internal Procedures*	The Task Force recommends that CDRH conduct an assessment of its staffing needs to accomplish its mission-critical functions.	We support this initiative.
4.1.2		CDRH should continue the integration and knowledge management efforts that are currently underway as part of the Center s FY 2010 Strategic Priorities.	

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4.1.3	**Leveraging external scientific expertise** *Internal Procedures*	CDRH should develop a web-based network of external experts, using social media technology, in order to appropriately and efficiently leverage external expertise that can help Center staff better understand novel technologies, address scientific questions, and enhance the Center s scientific capabilities.	An evaluation on the feasibility of social media technology for this purpose should be done in advance of commencing with this initiative. For example, this initiative would be difficult to implement if some external experts are not using social media technology. Also, use of social media raises concerns for how confidentiality will be maintained.
4.1.3		CDRH should assess best-practices for staff engagement with external experts and develop standard business processes for the appropriate use of external experts to assure consistency and address issues of potential bias.	
4.2.1	**Applying a Predictable Approach to Determine the Appropriate Response to New Science** *Internal Procedures*	CDRH should develop and implement a business process for responding to new scientific information in alignment with a conceptual framework comprised of four basic steps: (1) detection of new scientific information; (2) escalation of that information for broader discussion with others; (3) collaborative deliberation about how to respond; and (4) action commensurate to the circumstance — including, potentially, deciding to take no immediate action.	We generally support the proposed conceptual framework. FDA should work closely with industry and users when determining whether to escalate a signal for broader discussion. When ordering a Section 522 study, FDA should permit the manufacturer to withdraw the device if it determines it cannot afford the cost of the study. FDA should work closely with industry and users in the root cause analysis process. FDA should avoid forcing industry to change the design of a device in response to new scientific information; the company should make the determination of whether the best approach for mitigating a risk is to change the device design.
4.2.1		CDRH should enhance its data sources, methods, and capabilities to support evidence synthesis and quantitative decision making as a long-term goal.	We support the proposal to enhance data sources, methods and capabilities to support evidence synthesis and quantitative decision making.

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Section	Topic *Implementation*	Task Force on the Utilization of Science in Regulatory Decision Making Proposal	RTIB Response
4.3.1	**Promptly Communicating Current or Evolving Thinking to All Affected Parties** *Guidance/ Internal Procedures*	CDRH should continue its ongoing efforts to streamline its processes for developing guidance documents and regulation. CDRH should explore greater use of the "Level 1 – Immediately in Effect" option for guidance documents intended to address a public health concern or lessen the burden on industry. CDRH should also encourage industry and other constituencies to submit proposed guidance documents, which could help Center staff develop agency guidance more quickly.	We appreciate ongoing efforts to streamline its processes for developing guidance documents and regulations. We generally support the use of the "Level 1 – Immediately in Effect" option for guidance documents intended to address a public health concern or lessen the burden on industry.
4.3.1		CDRH should establish as a standard practice sending open "Notice to Industry" letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations on the basis of new scientific information. CDRH would generally issue "Notice to Industry" letters, if such letters constitute guidance, as "Level 1 – Immediately in Effect" guidance documents, and would open a public docket in conjunction with their issuance through a notice of availability in the Federal Register.	We are in favor of FDA publishing such "Notice to Industry" letters. RTI agrees that it is necessary for FDA to open a public docket in conjunction with their issue.
4.3.1		CDRH should take steps to improve medical device labeling, and to develop an online labeling repository to allow the public to easily access this information.	We are concerned with the proposal to develop an online labeling repository. FDA should caution the public that this information is for reference purposes only. The public should refer to the package insert and other labeling provided with the actual device for official information. Otherwise, the user might try to use a newer version of the package insert, which may not completely apply to an older product in their possession.

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Section	Topic *Implementation*	Task Force on the Utilization of Science in Regulatory Decision Making Proposal	RTIB Response
4.3.2	**Transparency about the Center's rationale for taking a particular course of action in response to new science** *Guidance/ Internal Procedures*	CDRH should develop and make public a Standard Operating Procedure (SOP) that describes the process the Center will take to determine the appropriate response to new scientific information, based on the conceptual framework outlined above.	We generally support this initiative and recommend that the proposed procedure be posted for industry comments before implementation.
4.3.2		CDRH should continue its ongoing efforts to make more meaningful and up-to-date information about its regulated products available and accessible to the public through the CDRH Transparency Website. In addition to the pre- and postmarket information that is already available on CDRH Transparency Website, the Center should move to release summaries of premarket review decisions it does not currently make public (*e.g.*, ODE 510(k) review summaries) and make public the results of post-approval and Section 522 studies that the Center may legally disclose.	We are not in favor of posting online FDA reviewers' summaries for cleared submissions. It may be impossible to redact reviewer summaries so that they pose no risk of disclosing proprietary information.

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September 28, 2010

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

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

Dear Sir/Madam:

On behalf of Biomet, Inc. ("Biomet"), a leading U.S. medical device manufacturer that, together with its subsidiaries, manufactures hundreds of 510(k)-cleared medical devices, I am pleased to submit these comments in response to the Center for Devices and Radiological Health ("CDRH" or "the Center") 510(k) Working Group Preliminary Report and Recommendations ("510(k) Working Group Report"), and the Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations ("Task Force on Science Report"). These comments are provided in response to the August 5, 2010, Federal Register notice and request for comments.

I. Summary Overview

As a manufacturer of hundreds of 510(k)-cleared medical devices, Biomet has had considerable experience utilizing the 510(k) program over the years. In light of this experience, and having carefully reviewed the preliminary reports released by the Working Group and Task Force that assess the 510(k) program and the utilization of science in regulatory decision making, Biomet supports CDRH's efforts to critically examine the 510(k) premarket notification process, with an emphasis on improving that process for all stakeholders.

As CDRH undertakes this effort, Biomet believes that it is important to identify and address critical, pervasive deficiencies before moving forward with any specific program modifications. This will help ensure that any changes to the 510(k) program are effective. The 510(k) Working Group Report establishes that the 510(k) review staff does not interpret regulatory requirements consistently. Indeed, this is an underlying deficiency that has been repeatedly identified with the 510(k) program over the years. Inconsistency in interpretation, and thus, application of

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regulatory requirements appears to stem in part from two root causes: (1) a lack of effective training in the regulatory requirements; and (2) a lack of clear agency guidance. Thus, Biomet generally supports proposals for clarifying existing guidance, developing additional guidance and improving the training of CDRH staff. Unless the issue of inconsistent interpretation of the regulatory requirements is addressed comprehensively and center-wide, there is no reason to believe that any changes to the program, whether proposed by CDRH or other stakeholders, can be effective. Along these lines, Biomet also supports efforts to gather more robust data on the operation of the 510(k) program itself. Such data will serve to identify underlying deficiencies so that effective changes can be designed and implemented.

As described in more detail below, Biomet supports CDRH's general efforts to examine the 510(k) program. In addition, Biomet supports the general concepts behind many of the recommendations, where the recommendations are presented in general terms. However, in the absence of known details about the recommended actions, Biomet must reserve the right to oppose specific proposals or approaches intended to implement these general concepts that may be formulated in greater detail in future guidance documents and/or proposed regulation.

While Biomet supports many of the recommendations set forth in the two reports, either in whole, in part, or with selective application, there are four key issues that Biomet cannot support: (1) consideration of off-label uses in the 510(k) review process; (2) an integration of the terms "intended use" and "indications for use" into a single term; (3) disallowance of the use of split predicates; and (4) requiring pre-clearance manufacturing inspections. These four issues are discussed in greater detail below. For the many other recommendations that Biomet has indicated general, conceptual or partial support, we believe that all necessary changes can appropriately be made through regulation and guidance alone. Statutory changes are not necessary to accomplish needed reforms.

Finally, Biomet has two significant concerns about the amount and scope of the changes recommended in the reports. First, Biomet has serious concerns about the potential negative consequences of implementing multiple changes to the 510(k) program within a short timeframe. It is Biomet's position that unless the transition is well-managed and changes are phased in over time with a limited number of non-controversial, high-priority changes implemented in the first phase, there will be considerable disruption to the 510(k) program. Second, the reports do not appear to have evaluated the resources – either financial or human – that will be needed to implement the recommended changes. As governmental resources are not unlimited, Biomet believes that before the Agency seeks to implement any change, that the Agency should assess the resources which will be needed to effectively implement the change and identify how the Agency intends to obtain the needed resources. FDA should also assess the substantive and resource impact of each proposed change on concerned stakeholders.

II. Working Group Recommendations

A. Recommendations Biomet Supports or Supports with Modifications

1. Additional Training for CDRH Staff

Biomet fully supports the provision of additional training for CDRH staff in their areas of scientific expertise, as well as on the statutory and regulatory requirements applicable to the

510(k) program. While enhancing scientific expertise is extremely important and Biomet supports this, the primary training deficiency established by the reports is the review staff's inconsistent interpretations of the Agency's own regulations. This specific aspect should be the focus of training efforts, allowing for the consistent interpretation and application of the Act and the regulations across the Center.

2. Providing Additional Guidance to Industry and Staff

Biomet supports the provision of additional guidance to CDRH staff and industry to improve the understanding, implementation and use of various aspects of the 510(k) program. Specifically, Biomet proposes development of additional guidance to industry and staff on the following topics:

1. The concept and definition of "intended use."
2. The types of device modifications that do, or do not, warrant submission of a new 510(k) notification.
3. The types of device modifications that are appropriately handled via a Special 510(k) notification.
4. The appropriate use of consensus standards, including the necessary documentation.
5. Standardization of 510(k) summaries.
6. Transfers of 510(k) ownership.
7. Circumstances under which clinical data will be required to support 510(k) clearance.
8. A standard operating procedure outlining the process that the Center will take to determine the appropriate response to new scientific information. With respect to this topic specifically, Biomet believes that any such procedure must include a clear definition of "new scientific information," as well as provide adequate due process, to allow concerned manufacturers to provide context for any perceived "new scientific information" and other relevant information.

Biomet supports the general concept of the development and issuance of guidance on the topics listed above, but reserves the right to oppose specific concepts or approaches to these topics, when the details of proposed regulations, guidance, or polices are disclosed by the Agency in the future.

3. Development of a Subset of Class II Devices

CDRH has proposed the development of guidance defining a subset of class II devices, called "Class IIb," for which clinical, manufacturing, and postmarket data may be required to support a substantial equivalence decision. Biomet generally supports the concept of establishing a small, focused subset of higher-risk class II devices that may be subject to additional requirements. However, we do not support the creation of a formal Class IIb category of devices, nor can we comment on this proposed Class IIb category without an understanding of: (1) the threshold for

placing a device in Class IIb; (2) which devices might be placed in Class IIb; and (3) whether other devices might be downclassified (for example, some types of hip and knee replacement devices would be good candidates for downclassification in light of a proposed subset of class II devices; see discussion below on the rationalization and harmonization of the regulation of hip and knee replacement devices). Biomet believes that clear criteria can be developed to define those limited circumstances when a particular device type will be subject to additional requirements without the need to create a new formal category that alters the existing classification scheme.

With regard to this potential subset of class II devices, CDRH should clearly define the circumstances under which additional requirements will be imposed, such as manufacturing information, clinical data requirements, and post-market requirements. Biomet believes that any additional requirements should be limited to higher risk devices where public health considerations justify the additional requirements. Clearly defining the type of clinical data which can support clearance for an established subset of higher-risk class II devices is critically important. Specifically, Biomet believes that the clinical data requirements for these devices should not rise to the level of clinical data required for PMA approval. In addition, any change which defines this small, focused subset of higher-risk class II devices should be handled as an administrative distinction, and should not be implemented as a new formal regulatory classification scheme or device class. This approach will ensure flexibility in the system to allow the movement of devices into and out of the subset, as safety profiles emerge.

Finally, Biomet does not support manufacturing and post-market requirements for all class II devices, but generally supports the development of guidance which clearly identifies the circumstances under which manufacturing and post-market information may be required for a focused subset of higher-risk class II devices. With respect to manufacturing information, such requirements would need to take into consideration that manufacturing processes may not be fully implemented at the time of 510(k) submission. As such, any requirement for manufacturing information should be limited to the company's plans to transfer the product to production – information that can be used to provide a baseline against which future changes can be assessed – and should not involve a pre-clearance inspection, as this would be overly burdensome and would delay the introduction of innovative technologies that will benefit patients.

4. Post-market Surveillance Studies as Condition of Clearance for Certain Devices

The 510(k) Working Group recommends that CDRH explore greater use of its post-market authorities, and potentially seek greater authorities to require post-market surveillance studies as a condition of clearance for certain devices. The 510(k) Working Group further recommends that, 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. Biomet supports the application of condition-of-clearance studies for only certain devices within the clearly-defined, focused subset of class II devices. For those limited devices which would be subject to this requirement, Biomet suggests that FDA should consider whether post-market surveillance plans developed to meet the requirements of the European Union ("EU") or other regulatory bodies adequately address the reasons for why FDA would request a condition-of-clearance study. Biomet does not support a requirement for post-market studies for all class II

devices, nor do we support increasing the Agency's authority to require such studies, such that post-market requirements become a new part of the 510(k) pathway.

5. Periodic Updates on Device Modifications for Certain Devices

The 510(k) Working Group Report 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). Biomet only supports this recommendation for a small, focused subset of higher-risk class II devices. Imposing this requirement for all class II devices would be unduly burdensome and would place tremendous strain on both industry and the Agency. A blanket requirement of this nature for all class II devices would require significant resources for industry, and would inundate FDA.

The recommendation also requires modification even if limited to the focused subset of class II devices. As this subset of class II devices would present a lower risk profile than class III devices, the frequency of such periodic reports should be less frequent than required for PMA-approved devices. Biomet suggests that an appropriate frequency would be every three years In addition, consideration should be given to phasing in this new requirement, and initially implementing the requirement only prospectively. In the event that such a requirement is implemented, it should include a fair, detailed process for resolving differences of opinion between the manufacturer and FDA. Without clear definitions and guidance, such a requirement will not improve the 510(k) process.

6. Improved Tracking of Program Metrics

The 510(k) Working Group recommends that CDRH should enhance its systems and program metrics to support continuous quality assurance. Biomet supports this recommendation. CDRH should develop metrics to continually assess its activities, needs, and challenges to ensure adequacy, accuracy, and efficiency in the following areas: (1) use of the 510(k) program; (2) use and development of internal data sources; (3) staffing needs; (4) audits of 510(k) review decisions; (5) quality of pre-submission interactions with industry; (6) root causes of existing challenges in IDE decision-making; and (7) ongoing integration and knowledge management efforts.

With respect to the recommendation to create ad hoc review teams to efficiently handle unexpected surges in workload, Biomet supports the general concept of ensuring capacity to respond to fluctuations in workloads. For this type of approach to be successful, however, the Center must ensure that: (1) teams are composed of appropriate types and levels of expertise; (2) there is appropriate oversight of these ad hoc teams, to ensure consistency in reviews; (3) review times in the branches providing resources to these ad hoc teams do not deteriorate; and (4) clear, transparent criteria are used to identify these "time-sensitive" priorities which would warrant creation of such ad hoc review teams.

7. Exploring the Implementation of Several New Policies

The 510(k) Working Group recommends that CDRH explore the implementation of various new policies. With respect to the recommendation to require 510(k) sponsors to submit detailed photographs and schematics of the device under review, Biomet generally supports certain aspects of this recommendation, but with limitations to ensure the protection of proprietary

information. Biomet does not support the recommendation to make schematics part of a public database. Photographs or depictions of a device that include proprietary information should not be released to a publically available website. Release of such information requires permission from the owner of that information. Biomet also believes that requiring such information may not be valuable in all reviews and suggests that CDRH consider whether there are certain device types for which this information would not enhance the reviews.

The 510(k) Working Group has also recommended an expansion of the use of "Level-1 – Immediately in Effect" guidance documents intended to address a public health concern or lessen the burden on industry, and development of a standard practice for use of "Notice to Industry" letters ("NTI letters"). Biomet applauds the general concept of using Level 1 guidance documents to address a public health concern and to lessen the burden on industry, and NTI letters to convey information when FDA has changed its regulatory expectations on the basis of new science. With respect to the first category, however, use of Level 1 guidance documents should be limited to significant public health issues. In addition, the Center should ensure that use of NTI letters are used to implement any changes to regulatory expectations uniformly, so as to avoid an unlevel playing field among competitors, where earlier market entrants are subject to lower standards. Biomet also suggests that the process for the development of NTI letters include a dialogue with concerned manufacturers to ensure that FDA is aware of information pertinent to the subject of the NTI letters before its issuance.

8. Reforming the Implementation of the De Novo Process

The 510(k) Working Group recommends reforming implementation of the *de novo* process. Biomet agrees that the *de novo* classification process requires reform. Existing guidance should be revised to incorporate a consistent evidentiary standard for *de novo* reviews. In addition, Biomet recommends that processes be put in place to allow sponsors to "concede" to the lack of an appropriate predicate, then to proceed to the merits of the *de novo* review so as to avoid unnecessary use of time and resources reviewing a 510(k) notice which will result in a not substantially equivalent ("NSE") determination.

B. Recommendations Biomet Opposes

1. Consolidating "Indications for Use" and "Intended Use"

The 510(k) Working Group Report proposes, as part of a broader recommendation to clarify the meaning of "substantial equivalence," consolidation of the concepts of "indication for use" and "intended use" into a single term, "intended use." Biomet opposes consolidation of these terms into a single term. Consolidation of these terms under the existing paradigm would dramatically limit the ability to demonstrate substantial equivalence, constrain the meaning of "intended use" and remove flexibility within the substantial equivalence paradigm. Limiting the flexibility of the system will, in turn, likely result in considerably more NSE determinations and an associated increase in *de novo* classification requests.

The two terms are not synonymous. Rather, the terms serve related but independent purposes in the realm of establishing substantial equivalence for market clearance and, once on the market, establishing the boundaries within which a company can appropriately market its products. Any

such change would create considerable confusion for industry with respect to the scope of off-label promotional restrictions, as well as for health care providers and consumers. Indeed, the indications for use statements required for 510(k)-cleared devices, as incorporated into manufacturers' labeling, are relied on by physicians to determine whether their use of the product is on-label or off-label.

While Biomet opposes the consolidation of the two terms, we fully support the development of additional guidance and clarification of both terms, particularly the term "intended use." Specifically, Biomet suggests amending 21 C.F.R. Part 807 to clearly define both terms. Once clarified, training of review staff on the meaning and application of these terms should be a Center priority.

2. *Disallowing Split Predicates*

The 510(k) Working Group Report proposes development of guidance on the use of multiple predicates and exploring the possibility of disallowing split predicates to establish substantial equivalence. While Biomet supports guidance on the use of multiple predicates, we oppose disallowance of split predicates. Disallowing split predicates will stifle evolutionary change, which the 510(k) program was designed to encourage. The ability to use split predicates, particularly for lower risk, novel devices, is fundamental to the definition of substantial equivalence. Disallowing them will result in unnecessary NSE determinations, creating substantial additional burdens for both industry and FDA. While the *de novo* process could be a potential pathway for such split predicate products, unless the *de novo* process is corrected, clarified and streamlined, it will not offset the negative impact on innovation from a policy which completely disallows the use of split predicates.

3. *Requirement to Provide List of All Scientific Information About the Safety or Effectiveness of the Device in the 510(k)*

The 510(k) Working Group Report proposes a requirement for all 510(k) submissions to provide a list and brief description of all scientific information regarding the safety or effectiveness of the device under review that should reasonably be known to the submitter. Biomet does not support this recommendation. A requirement to provide a list and brief description of all scientific information regarding the safety or effectiveness of all class II devices would be overly burdensome to industry and the Center. In addition, the purpose behind this recommendation, which appears to be an effort to obtain information not publically available, is adequately covered by the Truthful and Accurate Statement requirement for 510(k) notices. As written, the recommendation calls for a listing of "all" scientific information. It is unrealistic to expect that "all" scientific information can be identified; even the most thorough searches will miss some "known or reasonably knowable" information. Furthermore, once submitted, such information would constantly evolve and would no longer be current or "complete" at the time of the 510(k) clearance decision.

Biomet could support a requirement to submit additional technical and clinical information for a small, focused subset of class II devices, where the higher risk of these devices would justify the a need for enhanced information. The clinical information could be provided in the form of the clinical evaluation reports manufacturers prepare pursuant to the requirements of the European

Union, for products commercialized in that market. In addition to requesting the submission of technical and clinical information for the subset of class II devices, in the spirit of global harmonization, Biomet believes it would be reasonable for FDA to request information regarding the regulatory approval status of the devices in other GHTF Founding Member countries. These regulatory approvals outside of the United States, particularly those which result from a sophisticated review process (e.g. Design Examination Certificates for EU Class III products and Japanese approvals), should be an additional factor that FDA considers during its reviews. Of course, the clinical information would include available post-market information on the performance of the devices in such countries.

4. *Statutory Amendment to Provide Express Authority to Consider an Off-label Uses When Determining "Intended Use" in 510(k) Reviews*

CDRH recommends a statutory amendment to section 513(i)(1)(E) of the Federal Food, Drug and Cosmetic Act to provide FDA with express authority to consider an off label use, in certain limited circumstances, when determining the "intended use" of the device under review through the 510(k) process. Based on the language in the report, "limited circumstances" and "intended use" require clarification before Biomet can comment fully on this recommendation. However, at this time, Biomet does not support a statutory amendment giving the Agency express authority to consider off-label uses in 510(k) reviews. To begin with, the impetus for seeking this expanded authority is unclear. Off-label use of devices is not, *de facto*, unsafe. Indeed, off-label use of devices by physicians is often beneficial to patient care and, in some instances, becomes the standard of care. In fact, in a unanimous decision, the United States Supreme Court has acknowledged the importance of off-label use in *Buckman v. Plaintiffs' Legal Committee*, No. 98-1768, stating that " 'Off-label usage' of medical devices (use of a device for some other purpose than that for which it has been approved by the FDA) is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine." Therefore, off-label use of devices should not affect 510(k) clearance determinations absent compelling evidence that the primary use of the marketed device will be off-label. Off-label use is at a physician's discretion under the practice of medicine and, thus, beyond FDA's statutory authority. There are adequate existing authorities for FDA to address off-label promotion.

While Biomet does not support a statutory amendment, we do support development of clarifying guidance for reviewers on what can, and cannot, be considered in a 510(k) review. FDA currently has the authority to require labeling that a device should not be used for other uses outside of the cleared use.

Finally, Biomet respectfully disagrees with the stated concerns regarding the lack of availability of product labeling for physicians and consumers as a reason as to why the "substantial equivalence with limitations" paradigm may not provide sufficient protections against off-label use. Users are provided labeling with the product. In addition, many manufacturers routinely make their labeling accessible via the Internet. Expanding the Agency's authority to consider off-label uses during 510(k) reviews is not a fitting measure for protection from off-label use due to labeling availability issues.

5. *Requirement for Device Availability to FDA Review Staff During Review of Subsequent 510(k)s for Which the Device is a Predicate*

The 510(k) Working Group Report includes a proposed requirement for manufacturers to keep one device available for examination by FDA review staff during review of subsequent 510(k) notices for which the device is a predicate. Biomet could support this as a request (as opposed to a requirement), and only if limited to a review of the device in question and only if applied in situations where it is necessary to facilitating the review of a device. In this regard, it should be recognized that the devices available for review may only be prototypes, not final production units. Outside of these limited circumstances, the need for this requirement is unclear, particularly as it relates to the use of such devices during the review of competitors' devices. Such a requirement would be unduly burdensome (due to logistical issues with storage of large equipment and expiration of product) and costly.

6. Pre-Clearance Inspections

With regard to this suggestion by the 510(k) Working Group, Biomet strongly opposes the consideration of pre-clearance inspections for any class II devices as unnecessary and impractical. The benefit to be derived from this additional burden on FDA's inspection resources is unclear. Imposing such a requirement would add a tremendous burden on FDA's inspection resources and lead to delays in the clearance and, hence, the availability of innovative medical technologies. The vast majority of device manufacturers that would fall within the subset of class II devices are already subject to regular, periodic inspections of their manufacturing facilities. Such a requirement would require multiple inspections of the same facilities for manufacturers who regularly file 510(k) notices for devices in the focused subset of higher-risk devices.

7. Ability to Rescind 510(k) Clearance and/or Disallow Specific Predicates

The 510(k) Working Group Report recommends that FDA seek explicit authority to rescind 510(k) clearance and/or disallow specific predicates. Biomet does not support an extension of FDA's authority to rescind 510(k) clearance. Absent fraud in establishing substantial equivalence, rescission would not be justified and should not be allowed. If FDA could rescind a 510(k) for reasons other than fraud, the legal marketing status of each device that had subsequently relied on the rescinded device as a predicate would be called into question, even if the concerns that prompted the rescission do not apply to the subsequent devices. If a device is considered unsafe because it is manufactured incorrectly, or the manufacturer has unlawfully changed the design without meeting the appropriate premarket requirements, then FDA can take appropriate enforcement actions. These circumstances should not be used as grounds for revoking the original 510(k) decision. The Act already allows FDA to ban a device in cases of substantial deception or unreasonable and substantial risk of illness or injury. Banned medical devices can no longer be legally marketed and therefore, cannot be cited as a predicate device. If a device is substantially equivalent to a predicate that has not been banned, it is difficult to understand what other reasoning would justify rescission, other than fraud. Outside of these limited circumstances, undermining the predicate status of a device through rescission would not advance the public health.

C. Recommendations Requiring Clarification

1. Revise 2002 "Least Burdensome" Guidance

The Task Force recommends revising the 2002 "least burdensome" guidance to clarify the Center's interpretation of the "least burdensome" provisions of the Federal Food, Drug, and Cosmetic Act in light of the Center's position that the provision discourages appropriate requests for data. Biomet does not support this recommendation and challenges the stated concern underlying the recommendation. Review staff has, over the last two years, dramatically increased their requests for data, particularly with respect to orthopedic devices, as has been Biomet's experience. In orthopedics, the requests for additional information have resulted in a significant increase in the length of review times and a substantial decline in the number of clearances. In light of the apparent discrepancy between the stated reason for the recommendation and Biomet's experience, we request further clarification on the stated reason for this recommendation.

2. Define Scope of Authority to Rescind 510(k) Clearance

While the Agency's authority to rescind a 510(k), either fully or partially, is not explicit, FDA has rescinded 510(k)s in the past based on implicit authority. In light of this, Biomet requests further clarification on what the Agency considers to be its current authority to rescind a 510(k) for safety or efficacy reasons, and how the scope of this implicit authority might be altered via formal regulation. Absent this information, Biomet cannot comment on whether additional authority is needed.

3. Use of "Assurance Cases"

The 510(k) Working group recommends that the Center should develop guidance on how submitters should develop and use an assurance case to make adequate, structured, and well-supported predicate comparisons in their 510(k) notices. Assurance cases are not routinely used by the medical device industry in the U.S., or by FDA. Thus, the reason behind moving to this framework is unclear. In addition, the summary technical document ("STED"), or common technical document, is a format for information collection that exists and has been under pilot for years. The use of STED, which is in line with ongoing global harmonization efforts, appears to be a more logical direction. Biomet requires clarification on FDA's rationale for use of assurance cases, and the potential scope of their application. In the event FDA moved towards use of assurance cases, Biomet believes this method should be subject to a pilot program before widespread implementation and should only be used as an optional tool, not a required method for structuring submissions.

III. Additional Recommendations for Improving the 510(k) Process

1. Adopt GHTF Definition of Clinical Data

With regard to the type of clinical data required to support the substantial equivalence of a class II device, Biomet acknowledges footnote 163 of the 510(k) Working Group Report, which indicates that "the term 'clinical data' has not been defined through regulation or internal policy"

and that "there is not a consistent understanding within the Center regarding what type of information constitutes 'clinical data.'" Biomet recommends that FDA clearly define "clinical data" by adopting the GHTF definition of "clinical data," which includes both unpublished data and data on justifiably comparable devices, including the predicate device. See, GHTF Final Document, SG5/N1R8:2007, Clinical Evidence – Key Definitions and Concepts. Biomet notes that this definition is consistent with the regulatory definition of "valid scientific evidence" found at 21 C.F.R. § 860.7, and is sufficiently flexible to allow FDA to consider relevant clinical data derived from sources other than a full-scale premarket clinical study.

2. Explore Consideration of Foreign Approvals in GHTF Countries

At a minimum, Biomet believes FDA should consider foreign approvals as a factor in 510(k) determinations, particularly approvals from GHTF Founding States, which have been obtained after sophisticated reviews. Consideration of these approvals may allow FDA to lower the level of evidence required to clear such devices. Biomet believes that this would be appropriate in some cases, and encourages FDA to explore ways in which foreign approvals might be used in the review of 510(k) notices. Biomet proposes that FDA consider the concept of mutual respect of regulatory premarket determinations; unless FDA respectfully considers the results of premarket reviews by other regulatory bodies, other regulatory bodies may not appropriately respect FDA determinations. Recognizing that the public health agencies in all countries are seeking the same result – the availability of safe and effective innovative medical technologies to treat patients in their countries - such a concept allows for the efficient use of governmental resources among the GHTF Founding States. In the end, the convergence of regulatory requirements among the GHTF Founding States would benefit patients and conserve the limited resources of both government and industry.

3. Opportunity to Rationalize and Harmonize the Regulation of Orthopedic Devices

Biomet respectfully suggests that the current review and the consideration of additional information requirements for a small, focused subset of higher-risk class II devices provides a rare opportunity to rationalize and harmonize the premarket regulation of hip and knee replacement products. As CDRH clarifies its evidentiary and submission requirements for this subset of specific higher-risk devices, and becomes more comfortable with its ability to mitigate risk, Biomet respectfully suggests that the Agency down-classify some devices from class III, including total knee and hip replacement devices that currently require PMA approval.

The current state of regulation of knee and hip replacement devices in the United States should be rationalized. Devices with virtually identical risk profiles are regulated as either class II or class III. Thus, a hip prosthesis is classified as class III if the articulation is ceramic-on-ceramic or metal-on-metal but class II if the articulation is metal-on-polyethylene or ceramic-on-polyethylene. In reality, the risks posed by all of these articulations are very similar with the worst-case risk of failure, in virtually all instances, a revision surgery. For some hip and knee systems, certain components of those systems are classified into either class II or class III depending on what other components are used in the system. By way of example, a ceramic femoral head is class II when used in a system to articulate against a polyethylene liner but the identical femoral head is classified as class III when used in a system to articulate with a ceramic liner.

All hip and knee prostheses are properly treated within the subset of class II devices for which the Agency can establish additional premarket submission and postmarket information requirements. This would be consistent with the class III regulatory classification of such devices in the European Union, for which the submission requirements to obtain a Design Examination Certificate are greater than those currently required for 510(k) clearances but lower than that required for a PMA approval in the United States. Of course, such an approach would have the additional benefit of harmonizing the regulation of these device types in the United States and the European Union. It should be noted that Australia's Therapeutic Goods Administration ("TSA") has recommended harmonizing its regulatory treatment of these device types with Europe as well. See, TGA Request for Public Consultation on the Proposal for the Re-classification of Joint Replacement Implants dated October 23, 2009. Biomet and other orthopedic device manufacturers have, in general, supported that harmonization proposal.

Biomet is one of the five largest suppliers of orthopedic devices to the world market, with manufacturing facilities in the United States, Europe and Asia. Along with Zimmer, Inc., Stryker Orthopedics, Inc., Depuy Orthopedics, a division of Johnson & Johnson, Inc., and Smith & Nephew, Biomet supplies approximately 90% of the worldwide market of total knee and hip replacement implants. As FDA is aware, in compliance with European Commission Directive 2005/50/EC, issued on August 11, 2005, reclassifying total joints to Class III devices, Biomet and the other manufacturers undertook a four-year process of preparing the necessary design dossiers to obtain Design Examination Certificates (most total knee and hip replacement implants are CE-marked utilizing the conformity assessment process defined within Annex II.4 of the Medical Device Directive and thus subject to the transition period which ended on September 1, 2009). The regulatory process for obtaining these certificates was extremely thorough. Most of the major manufacturers utilized the British Standards Institute (BSi) as the notified body for the review of the overwhelming majority of their design dossiers. BSi used a thorough process for reviewing the design dossiers, often asking multiple rounds of questions before submitting the dossiers for Panel consideration. The review process for the typical design dossier review took many months to complete. BSi's review process, in turn, was closely monitored and audited by the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA). In sum, the collective effort of the manufacturers, the notified bodies and Europe's Competent Authorities to complete the reclassification was thorough and impressive, and establishes the safety and effectiveness of the devices which received Design Examination Certificates. As indicated above, the process utilized to obtain a Design Examination Certificate requires the submission of more types of information than required to obtain 510(k) clearance, but not the level of clinical evidence typically required to gain PMA approval.

For its part, Biomet prepared over 100 design dossiers for its devices sold in the European Union and expended considerable resources in the process. These dossiers document Biomet's compliance with the European Union's Essential Requirements, including risk assessment documentation and a clinical evaluation written and reviewed by qualified experts. The clinical evaluations were prepared pursuant to MEDDEV 2.7.1 "Evaluation of Clinical Data: A Guide for Manufacturers and Notified Bodies", and include a comprehensive review of available literature, data from various National Joint Registries, as well as published and unpublished clinical data from other internal and external sources. The Design Examination Certificates which resulted from the EU's reclassification process, represent a thorough and systematic

review by a qualified Notified Body, and provide reasonable assurance of the safety and effectiveness of the devices.

Biomet respectfully submits that placing knee and hip replacement devices in the proposed subset of class II subject to additional information requirements, considering the clinical evaluation reports required by the EU design dossiers as well as the Design Examination Certificates issued by Europe's Notified Bodies, while down-classifying the knee and hip devices currently classified in class III in the United States, would achieve a rational and globally harmonized standard for the classification for such devices. Such an approach would also provide reasonable assurance of the safety and effectiveness of the hip and knee devices used to treat patients in the United States.

IV. Conclusion

Biomet supports CDRH's efforts to critically examine the 510(k) premarket notification process, with an emphasis on improving that process for all stakeholders. Biomet supports a robust, flexible, program that strikes an appropriate balance between protecting the public health and medical device innovation. While certain aspects of the existing 510(k) program warrant strengthening, Biomet remains concerned about the potential negative consequences of implementing multiple changes to the 510(k) program within a short timeframe. Biomet urges FDA not only to assess the issues critically, and in light of input from all stakeholders, but to carefully and strategically approach implementation to maximize effectiveness and avoid unnecessary disruption.

We appreciate the opportunity to comment on strengthening the 510(k) premarket notification process as set forth in the 510(k) Working Group and Task Force Reports. Please feel free to contact us if we can be of further assistance.

Respectfully Submitted,

Robert E. Durgin

Senior Vice President, Quality/Regulatory/Clinical Affairs

Biomet, Inc.

To: Center for Devices and Radiologic Health

Re: Comments on Recommendations in CDRH Internal Evaluation Reports

From: Nancy Sauer, Director of Regulatory Affairs and Quality Assurance, Evergreen Research, Inc.

Date: September 30, 2010

I would like to thank CDRH for the effort and though that has gone into the internal evaluations regarding 510(k)s and other premarket submissions. I am respectfully submitting the following comments on the internal evaluation reports published in August 2010.

Recommendation	Comments
The Working Group recommends that CDRH explore the possibility of explicitly disallowing the use of "split predicates."	I agree that 510(k) submitters should not "cherry-pick" characteristics from the full universe of devices that have been cleared through the 510(k) process. I believe that some guidance from the agency on selection of appropriate and inappropriate combinations of predicate devices may be helpful. However, I would strongly recommend against an outright ban on the use of split predicates. Some very reasonable, useful, and well-understood new devices might be unnecessarily locked out of the 510(k) route to market. One case that I think illustrates an appropriate use of split predicates is K051711. This submission used four different predicate devices. There was significant overlap in the technology and intended uses of the four predicates, but no single device had all the required characteristics. This submission included data from a clinical study, to rule out the possibility that the combined characteristics could create unforeseen problems.
CDRH should reform its implementation of the de novo classification process to provide a practical, risk-based option that affords an appropriate level of review and regulatory control for eligible devices.	I would strongly encourage the Center to streamline the de novo classification process and to more clearly define the center's thinking on what constitutes a low-to-moderate risk device and the types of data needed to support claims of clinical utility. I know from experience with start-up companies that the current two-step process, the minimal guidance, and the uncertainty around the likelihood of success all discourage companies from considering de novo reclassification.
Require regular periodic updates on device changes that did not trigger a 510(k) and regular submission of current labeling, perhaps as part of annual registration and listing.	My opinion is that this requirement would be too burdensome for both industry and the center. If these reports are to have any value, FDA resources will have to be devoted to reviewing them. It is unclear how this would be accomplished without pulling resource away from new premarket submissions. The intent of these recommendations seems to be to ensure ongoing compliance. In my opinion, this type of oversight could be better accomplished by timely and effective establishment inspections.

Recommendation	Comments
CDRH should provide greater clarity about the circumstances under which it will require clinical data and provide greater clarity on the types of information that may constitute "clinical data."	Greater clarity would help companies plan their development, testing, and regulatory strategies. The guidance should be framed along broad principles rather than specific types of devices, though. In my opinion, it would be beneficial if FDA brought its definition of "clinical data" in line with that of Health Canada and European Notified Bodies. Ideally, a single clinical evaluation report should be able to meet the needs of regulators in all three of these major markets. Such reports would include a well reasoned combination of published clinical studies, demonstration of compliance with widely recognized standards, residual risk analysis per ISO 14971 (2007) and, where necessary, data from new clinical studies.
CDRH should explore the possibility of requiring each 510(k) submitter to keep at least one sample of the device under review available for CDRH to access upon request during review of the device itself or during future reviews in which the device is cited as a predicate	I would strongly discourage the center from adopting this recommendation, most particularly the idea that a manufacturer may need to submit a physical device when their product is cited as a predicate device. The requirement is not practical for many types of products. • In some complicated electromechanical products, there is no single configuration that is exactly "the 510(k)" configuration. • For products with limited shelf life, the need to account for aging effects raises many complications. • Where specific installation requirements or compatible devices are needed for correct function, the logistics of getting a reviewer access to the device are extremely complicated. • Finally, companies could potentially be required to maintain and provide samples of devices that they no longer market or support. The benefit of providing reviewer access to physical products seems marginal at best, and not commensurate with the burden on industry.
The Working Group recommends that CDRH develop guidance and regulations regarding appropriate documentation of transfers of 510(k) ownership and update the 510(k) database accordingly.	This would be a beneficial change in my opinion. Companies sell or license technology very frequently. A clear mechanism for showing current 510(k) ownership would help both industry and the center.
CDRH should develop guidance and SOPs to more clearly explain and to standardize the process for creating and assigning product codes.	This would also be a beneficial change in my opinion.

Recommendation	Comments
The Working Group recommends that CDRH consider requiring manufacturing process information in 510(k)s for at least some types of devices.	I do not believe that this would be a beneficial change. I believe that it would create additional burden for both industry and the reviewers, without any obvious benefit. It is not clear how manufacturing process data would be used to establish substantial equivalence. Manufacturing processes are not part of the core expertise of most ODE and OIVD reviewers.

Recommendation	Comments
Task Force recommends that CDRH revise its 2002 "least burdensome" guidance to clarify the Center's interpretation of the "least burdensome" provisions of the Federal Food Drug and Cosmetic Act.	It is unclear whether a change in the wording of the least burdensome guidance will change the dynamic around discussions of data requirements. CDRH staff have noted how often companies cite "least burdensome" language when they contest FDA data requests. I believe that this is because "least burdensome" is a recognized and codified phrase. It is not clear to me that the types of changes proposed by the Task Force will change how often companies contest FDA requests for additional data.
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 submissions.	Well-founded clinical evaluations are of benefit to all, including industry. I would encourage the center to think broadly when formulating recommendations about high-quality clinical data for medical device submissions. In some cases, compliance with device-specific standards and well-conducted literature reviews can be used appropriately to eliminate or minimize the size or scope of clinical trials.
CDRH should improve its mechanisms for leveraging external scientific expertise. The Task Force specifically recommends developing a web-based network of external experts, using social media technology.	I agree that providing easy mechanisms for reviewers to gain access to external scientific expertise is a valuable goal. I have concerns though about the proposal to use social network technology to accomplish that goal. There is a clear tendency for social networks to cluster around particular points of view. The potential for bias rather than balance in such networks seems very high. I would strongly encourage the center to build in strong review mechanisms to ensure scientific balance in these networks. Additionally, I would strongly encourage the center to maintain a high degree of transparency in their use of outside experts. I believe that the role of outside scientists, clinicians, or engineers in reaching certain decisions or making requests for more information should be disclosed to the manufacturer.

Recommendation	Comments
Task Force recommends that CDRH provide more transparency about their reasons for changes in data requirements or other changes in regulatory approach and that the Center should rapidly communicate those changes to affected companies.	I believe that these would be welcome and helpful changes. It is extremely discouraging to hear about new expectations or requirements after submitting a 510(k) or other premarket submission.

Thank you for your consideration of these comments.

Sincerely,

Nancy Sauer

BlueCross BlueShield Association

An Association of Independent Blue Cross and Blue Shield Plans

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September 30, 2010

Leslie Kux
Acting Assistant Commissioner for Policy
Food and Drug Administration
U.S. Department of Health and Human Services

Submitted via the Federal Rulemaking Portal: http://www.regulations.gov

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

Dear Ms. Kux:

The Blue Cross and Blue Shield Association (□BCBSA□) □representing the 39 independent Blue Cross and Blue Shield □Plans□that collectively provide health coverage to nearly 100 million, or one in three Americans □appreciates the opportunity to submit comments on the recommendations contained in the □Center for Devices and Radiological Health Preliminary Internal Evaluations,□as requested in the *Federal Register* on August 5, 2010 (75 Fed. Reg. 47307).

BCBSA strongly supports the FDA initiatives to evaluate and improve the 510(k) program. We clearly understand that the 510(k) process is a mechanism for regulating a high volume of medical devices in an efficient and timely manner.

However, as noted in our letter of March 17, 2010 □commenting in response to the FDA□s public meeting on February 18, 2010 □BCBSA has concerns about the regulatory process put into place by the 510(k) program. A major reason is that the BCBSA Technology Evaluation Center (an Evidence-based Practice Center contracted by the Agency for Healthcare Research and Quality), using well-established scientific review techniques and criteria, concluded that multiple products that had met FDA review standards and were permitted on the market were best considered investigational.

Thus, BCBSA is in general agreement with the majority of the more than 50 recommendations in the internal evaluations of the 510(k) process. We believe these recommendations will provide an effective overhaul of the program that will strengthen it, provide increased transparency and consistency, and result in decreased uncertainty for all FDA stakeholders about regulatory review criteria and outcomes.

We would give highest priority to the following five recommendations by the 510(k) Working Group for the CDRH:

1. **"Develop guidance defining a subset of class II devices, "called IIb" devices, for which clinical information, manufacturing information, or, potential evaluation in the postmarket setting, would typically be necessary to support a substantial equivalence determination."**

Creation of such a category would provide a clear statement of the value the FDA places on high quality evidence in decision making for novel or high risk devices.

2. **"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 reasonable known to the submitter."**

We would suggest that FDA consider requesting a comprehensive rather than a brief description of critical information on safety and effectiveness and that this information be considered of key importance in making decisions about whether new products should enter the marker or whether their predicates should remain in the marketplace. Paramount attention should be paid to assuring that FDA allows new products to enter the market only if their benefits outweigh their risks and they are likely to contribute to public health.

3. **"Consider adopting the use of an "assurance case" framework for 510(k) submissions**.

This is defined as a formal method for demonstrating the validity of claims by providing a convincing argument along with supporting evidence. We believe the use of this new regulatory tool would clarify the importance of looking beyond simple comparison of a new product to a predicate and would emphasize the value and importance for FDA to match claims to evidence in all of its regulatory decision making.

4. **"Explore greater use of postmarket authorities and potentially seek greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices."**

We recognize there are instances when FDA may find a product ready for market but in need of continued evaluation and tracking of device performance. We do not believe the mechanisms in place currently are strong enough to ensure high quality follow-up surveillance or to make certain that studies are performed in a timely and credible manner. In fact, postmarket information on products tends to be sparse, under analyzed, and to an extent hidden, which contributes to the moral equivalent of publication bias in terms of allowing products into the market with incomplete understanding of their public health impact.

5. **"Consider issuing a regulation to define the scope, grounds, and appropriate procedures, including notice and an opportunity for a hearing, for the exercise of**

authority to fully or partially rescind a 510(k) clearance. As part of this process, FDA should also consider whether additional authority is needed."

We recognize that for reasons ranging from changing technology and science to imperfect review practice and fraud, devices once marketed should be subject to market withdrawal. We strongly believe FDA should have authority to do this in a fair but timely manner and that the system for rescission should be clarified and enhanced.

Other recommendations that we believe deserve high priority include those that involve improving (1) guidance and limitations on use of predicates; (2) review transparency; and (3) administration, support, and training for good science.

We do have concerns about one of the Working Group's recommendations:

- **"Revise existing guidance to streamline the current implementation of the de novo classification process and clarify its evidentiary expectations for de novo requests."**

While we understand the value of this regulatory pathway for facilitating market entry of novel low risk devices, we believe in some cases FDA has allowed products to be processed as de novo submissions that are not actually low risk, and has taken worrisome short cuts in the scientific path used to establish performance. We urge FDA to proceed with care in changes it makes to this program; to be vigilant in reserving it for products that are clearly low risk; and to work to maintain quality science and decision making as it makes administrative changes to streamline de novo submissions.

BCBSA commends the FDA for the process it is using to solicit external input from all stakeholders. To the extent that FDA can effect changes in its program to strengthen the scientific base, improve the quality of decision making about which predicates can be used, and when to support new devices that provide public health benefit and avoid unnecessary harm, we believe these should be initiated in a timely manner. We recognize that while FDA review practices should be clarified and enhanced, attention should be paid to mechanisms to minimize or avoid unnecessary impediments to the development of important and valuable new technologies that do improve public health. The challenge to FDA now, as in the past, is to maintain balance in its work to promote and protect the public health by ensuring the benefits of medical devices outweigh their risks.

Finally, we would note that the CDRH preliminary internal evaluations beg a larger issue: the public utility of a regulatory program that operates by comparing products to a predicate device marketed before the arbitrary date of 1976, when the law establishing the 510(k) process was put into place; to a predicate that is not the best in the field; or to one that is distantly related to the new device through a series of intermediate predicates that represent fundamental changes in science and function.

We believe the public would be best served if FDA's review process for all devices were to be risk-based but grounded in principles of good science that ensure products can be used effectively by health care providers to improve patient outcomes and ensure patient safety. While a risk based and contingent system for gathering data to support new

product clearances makes sense, decision making should be made on the core tenets of safety and effectiveness as currently defined in FDA regulations, rather than the idea of showing simple equivalency to predicates of widely varying quality.

We recognize changes in this direction go beyond the scope of the internal FDA reports, and are hopeful that the Institute of Medicine will be successful in providing innovative and useful recommendations in policy, regulation, or law that may promote the ability of FDA to refine and improve its important mission.

We encourage FDA to continue to interact with its key stakeholders as it contemplates changes in its regulatory programs, seeking input on issues of transparency, on the 510(k) process, and on future regulation of laboratory-developed tests. By seeking outside input early in its processes for change, FDA is likely to make more informed and better decisions about what changes are most necessary and how to prioritize these.

We appreciate your consideration of our comments. These are difficult, challenging but exciting times in the life of the agency; we look forward to future opportunities to provide input to FDA on how it can continue to serve in its critical role as the world s premier medical authority for medical products. If you have any questions, please contact Naomi Aronson at (312) 297-5530 or Naomi.Aronson bcbsa.com.

Sincerely,

Allan M. Korn, MD, FACP
Senior Vice President Clinical Affairs and Chief Medical Officer

ASTRO
TARGETING CANCER CARE

October 4, 2010

Electronically submitted VIA: http://www.regulations.gov

Dr. Margaret Hamburg
Commissioner
Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Comments on Docket ID FDA-2010-N-0348; Request for Comments on 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 (75 FR 1501)

Dear Dr. Hamburg:

The American Society for Radiation Oncology (ASTRO) appreciates the opportunity to participate in this information-gathering process by offering comments to the Food and Drug Administration (FDA) regarding the Center for Devices and Radiological Health (CDRH) 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations (75 FR 1501). ASTRO commends the FDA's efforts to review the operation of the 510(k) program and the way CDRH uses science in its decision making process. Moreover, ASTRO supports the agency's goals in this review process of fostering medical device innovation, enhancing regulatory predictability and improving patient safety.

Introduction

ASTRO is the largest radiation oncology society in the world, with over 10,000 members who specialize in treating patients with radiation therapies. As the leading organization in radiation oncology, biology, and physics, the Society is dedicated to the advancement of the practice of radiation oncology by promoting excellence in patient care, providing opportunities for educational and professional development, promoting research and disseminating research results and representing radiation oncology in a rapidly evolving healthcare environment. ASTRO's priority is delivering the highest quality treatments for cancer and other serious medical conditions to patients.

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ASTRO Recommendations

ASTRO believes that the FDA's recommendations are generally well-thought-out and reasonable. We recognize that implementation of even a handful of the agency's proposals would significantly impact the process of bringing devices to market. ASTRO makes the following specific recommendations:

- ASTRO acknowledges that CDRH review staff do not currently have reliable ready access to meaningful information about past 510(k) decisions because there is no easily searchable internal database of detailed information on previous clearances. Accordingly, ASTRO endorses the work group recommendation that CDRH take steps to enhance its information systems and databases, utilizing input from experts in radiotherapy databases and stakeholder input, to provide easier access to more complete information about 510(k) devices and previous clearance decisions. The current CDRH 510(k) database lacks meaningful data to help device manufacturers identify adequate predicates, and we think an enhanced database would facilitate identification of a predicate device as well as determination of data support requirements.

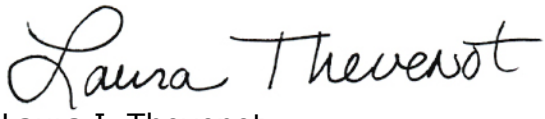
- ASTRO supports the working group recommendation that CDRH enhance its third-party reviewer training program and consider options for sharing more information about previous decisions with third-party reviewers to achieve greater consistency between in-house and third-party reviewers. ASTRO agrees that third-party reviewers should not be at an informational disadvantage compared to CDRH reviewers. Further, ASTRO advocates for the agency's periodic evaluation of the third-party program and enhanced attention to ensuring continuous quality assurance in the program.

- ASTRO further recommends that a usability assessment should be part of the 510(k) review. ASTRO recognizes the importance of human factors engineering in minimizing errors and sees a benefit to involving end users early in the development process to improve safety and mitigate use error. ASTRO advocates that usability of a device be addressed as well as functionality. Devices should be designed in such a way that "human factors" are considered, particularly with regard to intuitive and obvious operation. Moreover, because device users in many applications are operating several software/hardware devices concurrently, the context within which the user is operating the new/modified device should be part of the usability analysis. ASTRO believes the benefits of a "human centric" approach to development reach far beyond the end users.

Conclusion

ASTRO looks forward to working with the FDA on its efforts to streamline the process of bringing new safe and effective medical technologies to patients. ASTRO will provide additional comments to specific guidance documents and proposed rules as the FDA's review and modification of the 510(k) process evolves. Thank you for affording ASTRO this opportunity to provide comments on CDRH's 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations. Please contact Richard Martin at 703-839-7366 or richardm@astro.org if you have any questions.

Sincerely,



Laura I. Thevenot
Chief Executive Officer

TETHYS BIOSCIENCE

September 29, 2010

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

Re: Comments to the Docket No. FDA-2010-N-0348

To Whom It May Concern:

Thank you for the opportunity to comment on the Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations. At Tethys Bioscience, Inc. ("Tethys"), our goals are to identify those at highest risk for common diseases which will allow for early intervention opportunities to delay or potentially prevent disease onset. This may prevent severe health consequences as well as reduce health care costs. In 2008, we launched the PreDx™ Diabetes Risk Score (DRS), a multi-marker model based on a simple blood test that stratifies patients' risk of developing type 2 diabetes within five years. This test can help optimize patient care by providing physicians with a reliable tool to identify their patients who are at more imminent risk of developing diabetes and to direct them into an aggressive lifestyle intervention program.

As an *in vitro* diagnostic (IVD) test developer who anticipates completing a 510(k) process in the near future, we are especially vested in the process to review and update this regulatory pathway at the FDA. Based on the recommendations of the 510(k) working group, there are a number of issues in which we seek clarification and would like to provide input.

The 510(k) Working Group recommends that through the use of guidance, CDRH will create a "class IIb" device subset where additional data and information will be required for review and clearance. Additional data and information that may be requested include additional clinical, manufacturing and post-marketing data as well as the potential for requiring a pre-approval inspection. It is unclear how a 510(k) review process for a "class IIb" device will be different from a premarket application (PMA) process, since all but the post-marketing data are minimally required for PMA submission and approval. Will a guidance document be sufficient to define and clarify when each type of additional data will be required? Is a guidance document the best method to achieve a broad re-categorization of and data submission requirements for all medical devices?

This also points to the broader concern that the premarket review process for typical medical devices does not translate smoothly to in vitro diagnostics and creates additional challenges for the FDA to consider as they modify their 510(k) process. Diagnostics have different intended uses, indications for use, manufacturing operator or user requirements, and other factors that

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distinguish them from devices. Any review process should consider these and other factors, and Tethys believes that the FDA should have a separate process and criteria for reviewing IVDs.

More specifically, with regard to additional requirements of clinical data, the purpose of a 510(k) review is to establish evidence of safety and effectiveness, including strong analytical and clinical validity data. Recently, the FDA has begun requesting information about the clinical utility or usefulness of a diagnostic for novel moderate risk IVDs. The utility of innovative tests is often established post-marketing as payers, physicians and other stakeholders review and assess its value in their practice. If a test is innovative, it may not fit immediately into standard patient care. Clinical utility and usefulness will be determined by medical practice, reimbursement, education, publications, engagement with experts in the particular medical field, acceptance, and, ultimately, practice guidelines. Many of the most well-accepted diagnostic parameters, such as the level of glucose and, very recently, hemoglobin A1c to diagnose diabetes; cholesterol targets; and cardiovascular risk levels for high-sensitivity CRP, were set by the field, not by the test manufacturers.

The culmination of this process may even lead to the development of practice guidelines to recommend the integration of a new diagnostic into the standard of care. This process typically occurs once the diagnostic is on the market and hence, would be inappropriate to be included in regulatory review of its safety and effectiveness. We request that the FDA focus their efforts on safety and effectiveness of IVDs, and enable providers and payers to determine the value of the diagnostic in medical practice.

Lastly, the 510(k) Working Group has recommended that CDRH explore the possibility of pursuing a statutory amendment that would provide the agency with express authority to consider an off-label use when determining the "intended use" of a device under review. On what basis will the manufacturer be required to seek additional or different intended uses of a device than were originally planned by the manufacturer? This may cause undue burden in that it may require a substantial amount of time and resources prior to the clearance of a product for a use that the manufacturer had no intention of promoting. It may be the opinion of a reviewer that a different product or a different intended use may be more helpful in clinical practice. However the manufacturer has usually evaluated many scientific, medical, technical and business issues prior to developing and bringing a product to market. Tethys believes that the safety and effectiveness data, in addition to the appropriate warnings, precautions and limitations of the labeling should remain sufficient to inform users of the intended use of a device.

We appreciate and support the FDA's desire to develop a more predictable and transparent review and clearance process while improving patient safety and fostering innovation. Thank you very much for your consideration of these comments.

Sincerely,

Mickey S. Urdea, Ph.D.
Chief Executive Officer and Chairman
Tethys Bioscience, Inc.

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GALILMEDICAL
A New Vision of Precision

October 4, 2010

Via Electronic Mail

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

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

Dear Sir / Madam:

Galil Medical Inc. is pleased to provide our comments and recommendations on the Center for Devices and Radiological Health (CDRH) *510(k) Working Group Preliminary Report and Recommendations* and the *Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations.* Galil Medical is a global leader of state-of-the-art cryotherapy systems that employ novel hypothermic surgical technologies to destroy cancerous tissues. Our products are delivered through multiple physician specialties and offer highly effective and minimally invasive therapies for prostate, kidney and metastatic liver cancer. Below, you will find our comments on the CDRH reports, as well as corrections to some errors noted during our review of the reports.

Comments on CDRH Reports

Galil Medical supports FDA's efforts to streamline the 510(k) process to ensure that the 510(k) process provides reasonable assurance of safety and effectiveness of marketed medical devices and fosters innovation in the medical device industry, while trying to provide industry with as much of a predictable process as is practical. We have participated with both Advamed and LifeScience Alley (LSA) to provide comments and recommendations to the CDRH *510(k) Working Group Preliminary Report and Recommendations* and the *Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations* and our views are aligned with and in support of the comments and recommendations being submitted by both of these groups.

In addition to the comments and recommendations submitted by both AdvaMed and LSA, Galil Medical requests that FDA provide public notice and appropriate public comment periods for each recommendation that it intends to implement, whether a regulation change or a guidance change. We believe doing so would benefit both the FDA and interested stakeholders. The

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recommendations outlined in the *510(k) Working Group Preliminary Report* and the *Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report* were very broad and vague; making it difficult to provide valuable comments. With the exception of additional training for industry and FDA reviewers, any of the seventy-four (74) recommendations could have a positive or negative impact on industry and public health depending on how they are implemented. Therefore, in order for the process to be a truly collaborative process, it is imperative that FDA provide adequate public notice of intended changes and seek public comment with reasonable comment periods.

An example of this point is the recommendation on page 76 of the *510(k) Working Group Preliminary Report* to "…develop guidance defining a subset of class II devices, called "class IIb" for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting, would *typically* be necessary to support a substantial equivalence determination." It is unclear to industry which devices would be categorized into the new "class IIb" classification scheme and, therefore, it is impossible to provide substantive comment on this recommendation. Further, Galil Medical does not believe that a new classification of devices can be created without statutory change. **Galil Medical does not support the implementation of a new "class IIb" classification of devices and, instead, recommends that the FDA use risk-based decisions to determine if additional information is required to determine substantial equivalence. Galil Medical also notes that any group of devices that is determined to require additional information should be limited in size. That is, the FDA should not use the freedom of requiring additional information as the norm, but rather as the exception.**

Galil Medical is concerned that the cumulative implementation of all the proposed recommendations in the two reports would represent a significant and drastic change to the 510(k) process. Clearly, it would be overwhelming for both industry and FDA reviewers if all, or even a significant portion of the recommendations are implemented simultaneously.

In summary, Galil Medical requests that the FDA consider a phase approach when determining when and how to implement the chosen recommendations by implementing the changes incrementally in order to prevent overburdening the agency as well as industry and other stakeholders.

Discussion of Noted Errors

In addition to the aforementioned comments, Galil Medical noted several incorrect statements in the Case Study: "Intended Use" on pages 47 and 48 of the *510(k) Working Group Preliminary Report.* We request that the FDA consider the comments below and publish a correction notice as soon as reasonably possible. This case study presents a history of the use of cryosurgery for the treatment of prostate cancer. The impact statement of this case study contains several errors and implies to the reader that cryosurgery is not a viable treatment option for the treatment of prostate cancer. A reader outside the industry that is not familiar with this procedure would likely perceive that the FDA has been particularly lenient on cryosurgical device manufacturers. This in fact has not been the case at all. Each misleading notion along with the corrections are outlined below.

1. The *510(k) Working Group Preliminary Report* states "Cryosurgery has not been recognized by the American Urological Association as a recommended therapeutic option

for prostate cancer." The reference cited for this statement is (103) American Urological Association, "Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update" (2007/2009). Available at http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main- reports/proscan07/content.pdf.

Correction: The cited reference does not state that cryosurgery has not been recognized by the American Urological Association (AUA) as a recommended therapeutic option for prostate cancer. In fact, the report doesn't address cryosurgery as a treatment option and specifically states, "Cryosurgery for the treatment of localized prostate cancer will be the topic of a forthcoming AUA best practice policy."

It should also be noted that the cited reference from 2007 is not the most current reference published by the AUA. In 2008, the AUA published a Best Practice Policy Statement titled "Cryosurgery for the Treatment of Localized Prostate Cancer.[1]" This most recent best practice statement contains the following specific statements, which clearly contradict the statements in the FDA case study.

- Page 3: "Additionally, prostate cryosurgery has been found to result in acceptable HRQL-based outcomes with a reduced cost when compared to other local therapeutic options."
- Page 7: "In summary, a review of the historical evolution of cryosurgery provides two overriding messages, the first being that there is evidence of therapeutic benefit, and the second, that treatment-associated morbidity has been reduced as technological refinements have emerged."
- Page 7: "Clinically, cryosurgical procedures are grounded on well-recognized scientific principles supporting physician-managed destruction of clinically-localized tumors of the prostate."
- Page 11: "The consensus opinion of the Panel is that primary cryosurgery is an option, when treatment is appropriate, to men who have clinically organ-confined disease of any grade with a negative metastatic evaluation."
- Page 20: "It is the opinion of the expert Panel that salvage cryosurgery can be considered as a treatment option for curative intent in men who have failed radiation therapy."
- Page 30: "Cryosurgery guided by ultrasound and temperature monitoring is an option for recurrent clinically organ-confined prostate cancer after radiation therapy. As with other salvage therapies for curative intent, cryosurgery should be considered early for patients defined as radiation failures."

Additionally, J Rees et al reported that the AUA recognized cryoablation as a therapeutic option for prostate cancer as early as 1996[2]. In 2000, the AUA published a position statement on their website that stated cryosurgical ablation of the prostate for patients who fail radiation therapy for prostate cancer is a treatment option. This position statement was subsequently replaced with the 2008 Best Practice Policy Statement[1].

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[1] American Urological Association, "Best Practice Policy Statement: Cryosurgery for the Treatment of Localized Prostate Cancer," 2008. Available at http://www.auanet.org/content/media/cryosurgery08.pdf.

[2] J Rees, B Patel, R MacDonagh, R Persad. Cryosurgery for prostate cancer. *BJU International* 2004; **93**: 710-714. Available at http://onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2003.04746.x/pdf.

2. The 510(k) Working Group Preliminary Report states "The Centers for Medicare and Medicaid Services (CMS) were slow to reimburse for the use of these cryosurgical devices for treatment of prostate cancer; reimbursement was not effective until 2001." The reference cited for this statement is (104), Centers for Medicare and Medicaid Services, Medicare Hospital Manual, Transmittal 774 (June 11, 2001). Available at http://www.cms.hhs.gov/transmittals/downloads/R774HO.pdf.

   Correction: This statement is inaccurate. The first national coverage decision by CMS was issued in 1999 for prostate cryoablation as a primary treatment for stages T1-T3[3]. In 2001 CMS expanded the coverage for salvage cryotherapy for patients who had a failed trial of radiation as a first line treatment and with specific clinical indicators for Tumor Staging, Gleason Score and PSA[4].

   In fact, the transmittal cited in the FDA report states,

   "Medicare will cover cryosurgery of the prostate gland effective for claims with dates of service on or after July 1, 1999. The coverage is for:

   1. Primary treatment of patients with clinically localized prostate cancer, Stages T1-T3 (diagnosis code is 185 - malignant neoplasm of prostate). Cryosurgery of the prostate gland, also known as cryosurgical ablation of the prostate (CAP), destroys prostate tissue by applying extremely cold temperatures in order to reduce the size of the prostate gland (procedure code 60.62 - perineal prostatectomy (the definition includes cryoablation of prostate, cryostatectomy of prostate, and radical cryosurgical ablation of prostate).

   Claims for cryosurgery of the prostate gland should meet the requirements that the cryosurgery be performed only as a primary treatment for patients with clinically localized prostate cancer, stages T1-T3.

   2. Salvage therapy (effective for claims with dates of service on or after July 1, 2001)
      - Having recurrent, localized prostate cancer;
      - Failing a trial of radiation therapy as their primary treatment; and
      - Meeting one of these conditions: State T2B or below; Gleason score less than 9; PSA less than 8 ng/ml."

Galil Medical can only assume that the errors in the case study were based on both inadequate and outdated information. It would appear as if the FDA used the inaccurate information to justify the recommendation to combine the terms "Intended Use" and "Indications for Use". However, since the facts upon which the justification to do so were misstated, the cited case study is no longer valid. Further, the publication of the case study presents a misleading picture

[3] Decision Memo for Cryosurgery Ablation for Prostate Cancer (CAG-00031N). Available at https://www.cms.gov/mcd/viewdecisionmemo.asp?id=81.

[4] Decision Memo for Cryosurgical Salvage Therapy for Recurrent Prostate Cancer (CAG-00064N). Available at https://www.cms.gov/mcd/viewdecisionmemo.asp?id=20

to reviewers of the report that are not familiar with the specific information regarding the cryoablation technology 510(k) clearances. Additionally, the misstated case study presents speculation that the cryosurgical device manufacturers took advantage of the FDA process. Galil Medical strongly urges the FDA to publish a correction to this misleading information as soon as reasonably possible.

In conclusion, Galil Medical would like to reiterate its support of FDA's mission to improve the 510(k) process. We encourage the FDA to seriously consider not only the specific comments we have outlined above for the cryoablation technology but also the comments and recommendations made by both Advamed and LSA. We stand ready to discuss and work directly with the agency as the FDA moves forward with this initiative. We look forward to providing comments on future specific proposals to address each recommendation that FDA chooses to implement. Please do not hesitate to contact me if I can be of further assistance to the FDA regarding the Galil Medical comments; I can be reached at 651-287-5096 or via email at *amy.mckinney@galilmedical.com*.

Sincerely,

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Division of Dockets Management (HFA –305)
Food and Drug Administration
5630 Fishers Lane - Room 1061
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Submitted via www.regulations.gov

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 [Docket FDA-2010-N-0348]*

Dear Sir or Madam:

Abbott Laboratories submits the following comments regarding the Center for Devices and Radiological Health (CDRH) 510(k) Working Group Preliminary Report and Recommendations and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations published in the Federal Register on August 5, 2010 at 75 FR 47307.

Abbott Laboratories is a global, broad-based health care company devoted to discovering new medicines, new technologies and new ways to manage health. Our products span the continuum of care, from nutritional products and laboratory diagnostics through medical devices and pharmaceutical therapies.

We appreciate CDRH providing stakeholders this opportunity to submit input on the recommendations discussed in these reports, including the feasibility of implementation and potential alternatives. FDA has described these recommendations as preliminary[1], and, as such, many of the recommendations would require more detail to appreciate their full regulatory impact. Therefore, we request FDA provide ample opportunity for stakeholders to comment on specific policies, guidance, and regulations followed by thorough agency review and consideration of comments prior to finalization.

[1] 75 FR 47307

As CDRH evaluates which recommendations to pursue, we believe improvements to the following areas are necessary to implement and will benefit all stakeholders:

- increasing training for reviewers, managers, and industry,
- strengthening the *de novo* process,
- revising existing guidance on device modifications that warrant or do not warrant submission of 510(k),
- standardizing a template for 510(k) summaries
- establishing a process for notification of transfer of ownership of 510(k)s, and
- enhancing CDRH's scientific capabilities through collaborative mechanisms to leverage access to experts.

These items are addressed in greater detail in the following comments and are organized in the order the recommendations appear in the two-volume report.

Volume 1: 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.

Specific recommendations pertaining to "same intended use": (1) consolidate into a single term the terms "intended use" and "indications for use," (2) rename the "indications for use" statement, (3) develop or revise guidance to identify the characteristics to include in the concepts of "intended use," and (4) provide training to reviewers, managers, and industry.

While we agree with the agency that clarification of the terms "intended use" and "indications for use" will benefit reviewers, managers, industry, and the 510(k) process in general, we do not agree with the recommendation to consolidate the two terms into a single term.

Consolidating the two concepts into one term will likely constrain the meaning of "intended use" and reduce the agency's current flexibility. Differentiation of the two terms serves the purpose of a clearer identification of the data requirements for demonstrating substantial equivalence. Further, both terms have a long-standing history of use in determining substantial equivalence.

Thus, we recommend the agency keep the two terms separate, but clarify the use of the terms within the context of making a determination of substantial equivalence. We recommend the agency more explicitly define intended use, which is the use of a generic type of device, and indications for use, which more specifically describes the device's function.

Intended use determines the boundaries of use for a generic type of device and is constructed to encompass the appropriate breadth of use for which the regulatory controls for the generic device type continue to provide reasonable assurance of safety and effectiveness. It refers to the objective intent for the device function of the persons

legally responsible for the proposed labeling of the device and describes what the device is intended to provide to the user and patient and for what purpose(s).

The indications for use provides a detailed, specific description of target population(s) for the intended use that is a general description of device function, and includes, as appropriate, the disease or condition the device will diagnose, treat, prevent, cure or mitigate and/or a description of the patient population for which the device is intended.

Any clarification of the definition of these terms should be just that, a clarification, and not an alteration of the meaning of these terms as they have been historically interpreted and applied by FDA and product manufacturers. Further, we believe that clarification of these two terms should be forward-looking, and that the agency should not retroactively apply the refined definitions of these terms. Such an approach may divert agency resources without public health gain.

We agree with the need to train reviewers, managers, and industry as FDA adds clarity to these two terms. Additionally, any modifications to clarify the meaning and application of the terms "intended use" and "indications for use" should be subject to public notice and comment given the long-standing use of both terms in determining substantial equivalence, as well as the potential for significant impact to the 510(k) process should the modifications result in reducing how intended use is used to determine predicates to the 510(k) process.

Specific recommendations pertaining to "different questions of safety and effectiveness:" (1) reconcile language in 510(k) flowchart and statute regarding "different technological characteristics and "different questions of safety and effectiveness," (2) revise guidance to provide clear criteria for identifying "different questions of safety and effectiveness" and identify a core list of technological changes that generally raise such questions, and (3) provide training for reviewers, managers, and industry on these topics.

In assessing substantial equivalence of a new device with the same intended use as the predicate, but possessing different technological characteristics Section 513(i)(1)(A)(ii) of the FD&C Act provides: (1) the information submitted demonstrates that the device is as safe and effective as a legally marketed device and (2) does not raise different questions of safety and effectiveness than the predicate.

FDA "Guidance on the CDRH Premarket Notification Review Program," K86-3 (June 30, 1986) incorporates this assessment as an element of the flow chart illustrating the 510(k) Substantial Equivalence Decision-Making Process. The step of the flow chart asking "could the new [technological] characteristics affect safety or effectiveness" represents a correct interpretation encompassed within the statutory language to assess whether the device possessing different technological characteristics is as safe and effective as a legally marketed predicate. Similarly, the next question on the flow chart, "do the new characteristics raise new types of safety or effectiveness questions" represents a correct interpretation of the statutory language "does not raise different questions of safety and effectiveness than the predicate device." Because the flow chart is an application of the statutory language reconciliation of the language is not warranted.

Further, as identified in the report, this framework and these guidelines from 1986 are still in use by CDRH today[2]. Because of the long-standing and well-established interpretation and application of the statutory language as described in the flow chart, a new interpretation would alter the framework for establishing substantial equivalence.

As a result, such a change is more than a reconciliation of language, but a new interpretation and application of FDA's long-standing framework and interpretation. Any such changes should be addressed via a public notice and comment period.

Rather than revise long-standing agency interpretation of statutory language, we recommend the agency provide increased clarity and consistency in assessing when different technological characteristics raise different questions of safety and effectiveness. We also recommend the agency refine its current process for identifying different questions of safety and effectiveness, such as unknown or new risks, by relying on the product risk assessment or hazard analysis to make this determination. While guidance can be used to identify broad categories of different technological characteristics, such as those identified in statute, significant change in the material, design, or energy source, the assessment of different questions of safety and effectiveness may be more difficult to address in a comprehensive manner. Use of the product risk assessment or hazard analysis is an effective means for facilitating this analysis.

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.

Specific recommendations pertaining to valid, well-reasoned predicates: (1) guidance identifying devices that should no longer be available for use as a predicate because of safety and/or effectiveness concerns, (2) 510(k) rescission authority, (3) guidance on the appropriate use of "multiple predicates," (3) disallowance of "split predicates," (4) update bundling guidance to distinguish between multi-parameter or multiplex devices and bundled submissions, (5) training for reviewers and managers on reviewing 510(k)s that use "multiple predicates,"(6) assess the impact of submissions for multi-parameter or multiplex devices and bundled submissions on review times, and (7) conduct additional analysis of 510(k)s citing more than five predicates.

Under 513(i)(2) of the FD&C Act, only those devices removed from market by FDA or deemed adulterated or misbranded by a judicial order are disqualified from being predicate devices. Thus, guidance is not the appropriate means for disqualifying a device as serving as a predicate.

Rather than focusing on disqualifying devices as predicates, which creates numerous issues due to the iterative nature of device development and the core element of the 510(k) process as a system that relies on previous devices or predicates to further the introduction of device developments, we recommend the agency focus its efforts on educating stakeholders of the role of the predicate, which is to classify the new device.

[2] *See* CDRH 510(k) Working Group Preliminary Report and Recommendations at 26.

Guidance defining terms such as multiplex, multiple, and split predicates would benefit all stakeholders and we agree with the usefulness of providing guidance defining these terms. Bundling increases efficiencies in the review process. We believe the topic of bundling is adequately addressed in FDA guidance, "Bundling Multiple Devices or Multiple Indications in a Single Submission" (June 22, 2007). Due to the relatively recent release of this guidance, we do not believe updating this guidance is needed at this time. Increased reviewer and industry training on the practice of bundling is recommended. However, should FDA modify this guidance, we recommend it continue to adhere to the following principles, articulated in the existing guidance, regarding the areas in which it is appropriate to bundle:

(1) devices within the same generic device type,
(2) similar indications,
(3) reliance on similar data,
(4) whether primarily one review division/group will review the devices, and
(5) in the case of in vitro diagnostic devices, the guidance document specifically identifies the following as acceptable bundling practices: (a) the bundling of multiple analytes or instruments when the same analytical and clinical data can be used for the analytes/instruments referenced (e.g., drugs of abuse panel), (b) assayed controls and/or calibrators used with an assay(s), (c) multiple reagents intended to be used together to obtain a profile (e.g., cardiac panel), and (d) similar sample matrixes (e.g., serum, plasma).

Disallowance of split predicates is not in line with the statute, which provides for demonstrating substantial equivalence when the intended use is the same as the predicate and the different technology does not raise new/different questions of safety and effectiveness. Submission of information pertaining to a device with the same technological characteristics as the new/different device may aid in the assessment of whether new questions are raised, and thus the concept of providing information about a device, in and of itself, using the same technology as the new device should not raise concerns.

We agree that training reviewers, managers, and industry on the use and application of terms associated with the 510(k) process is important to facilitating the process.

Lastly, should FDA move forward and conduct assessments, such as that discussed in the 510(k) Report to assess devices cleared with five or more predicates, it would be beneficial to publicly release these assessments with an opportunity for comment, if a change in practice is recommend as the result of the assessment.

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

Specific recommendations pertaining to de novo: (1) streamline current implementation of de novo classification process and clarify evidentiary expectations, (2) encourage pre-submission engagement between submitters and reviewers, (3) explore establishing a generic set of controls that could use as baseline special controls for device classified into class II through the de novo

process, which could be augmented with additional device-specific controls as needed.

Strengthening and optimizing the *de novo* process through a well-defined regulatory pathway will benefit the agency, industry, and patients. This underutilized process has the potential to play a key role in the regulation of medical devices, lacking a predicate, for which general or special controls provide a reasonable assurance of safety and effectiveness.

A streamlined process for assessing which devices are eligible for review under the *de novo* process could begin with an assessment of the reason, due either to (1) the lack of a predicate with the same intended use or (2) the same intended use but new technology as compared to the named predicate device(s) raising new/different questions of safety and effectiveness. The assessment could continue with a flow chart for assessing eligibility based on principles of risk management or the utilization of device classification rules, such as those produced by the Global Harmonization Task Force (GHTF). GHTF documents "Principles of Medical Devices Classification"[3] and "Principles of In Vitro Diagnostic (IVD) Medical Devices Classification"[4] provide internationally harmonized classification rules, which may be a useful tool in assessing eligibility for *de novo* review.

Once it has been determined that the device is a likely candidate for *de novo* review, there should be a provision for a pre-submission meeting between the applicant and the agency to review key items, such as the decision process leading to the determination the device is eligible for *de novo* review and the submission evidentiary expectations based on a generic set of controls for *de novo* applications. Clear guidance as to the timing and content of the meeting would benefit the process. As identified in the report, a generic special control for devices reviewed under *de novo* is another good step to strengthening the process. A generic set of special controls modeled after the essential principles of the Global Harmonization Task Force (GHTF) provide a means to create a consistent evidentiary standard for *de novo* review.

We recommend evaluating the adoption of the essential principles of safety and performance produced by the GHTF in "Essential Principles of Safety and Performance of Medical Devices,"[5] as the standard for special controls for Class II *de novo* devices.

Further, to increase consistency in the process we recommend the creation of a template to guide the submission content and review, such as the use of the summary technical document or STED, as described in the GHTF document "Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED).[6,7]"

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[3] GHTF document, "Principles of Medical Devices Classification (GHTF/SG1/N15:2006) is available at http://www.ghtf.org/documents/sg1/SG1-N15-2006-Classification-FINAL.pdf

[4] GHTF document, "Principles of In Vitro Diagnostic (IVD) Medical Devices Classification (GHTF/SG1/N045:2008) is available at http://www.ghtf.org/documents/sg1/sg1final_n045.pdf

[5] GHTF document, "Essential Principles of Safety and Performance" (GHTF/SG1/N41R9:2005) at http://www.ghtf.org/documents/sg1/sg1n41r92005.pdf

[6] GHTF document, "Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)" (GHTF/SG1/N011:2008) is available at http://www.ghtf.org/documents/sg1/sg1final-n11.pdf

Again as noted in the report, we agree there is merit in minimizing the time spent on the 510(k) review for a product that clearly is *de novo*. Consideration should be given to eliminating the need to submit a 510(k) and receive an NSE determination before initiating the *de novo* review.

In implementing this new approach, we recognize the need for training of industry and FDA reviewers and the identification and implementation of metrics designed to assess the effectiveness of the process.

Such an approach offers the opportunity to create a more consistent, rule based system to evaluate medical devices, and further international harmonization consistent with FDA's role as a founding member of the GHTF.

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.

Specific recommendations pertaining to unreported device modifications: (1) revise existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k) and for modifications requiring new 510(k) specify which are eligible for a Special 510(k) and (2) regular periodic updates to CDRH listing any modifications made to a device and why each modification does not warrant a new 510(k) phased in for "class IIb" subset and expanded to a larger set of devices over time.

We agree with the need to update existing guidance, "Deciding When to Submit a 510(k) for a Change to an Existing Device" (January 10, 1997) to further clarify what types of modifications do or do not warrant submission of a new 510(k). While we agree this guidance is due for an update, this is a good guidance that has proved useful to FDA and industry over the years. The use of the flow charts to assess changes has been especially helpful and should remain. Consideration of the risk evaluation process as a means to assess changes rising to the level of a new filing, guidance for evaluating the totality of changes made since the last clearance, and additional guidance pertaining to the evaluation of incremental manufacturing changes are recommended areas for improvement as the document is revised.

In revising the guidance, we believe it would be helpful to delineate the types of changes eligible for review as a Special 510(k), such as those discussed in the guidance, "The New 510(k) Paradigm: Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications" to improve the consistency of the Special 510(k) review process. We note the use of the Special 510(k) is more akin to the filing of a supplement for a PMA-approved device than a 510(k) for a new device, as the Special 510(k) is used to implement a change to the sponsor's own cleared device. Consideration of this

[7] We note the GHTF is currently engaged in the development of a STED document for in vitro diagnostic medical devices, in which the public comment period closed January 7, 2010.

element may assist the agency as it delineates the types of changes eligible for review as a Special 510(k).

In regards to regular periodic updates listing device modifications made to a device and why each modification does not warrant a new 510(k), we believe efforts focused on revising the existing guidance for assessing product changes would result in more tangible program improvements in regards to modifications to existing medical devices. This approach is preferable to establishing an infrastructure to receive and review periodic reports for all class II devices to address modifications on an individual device or company basis. Rather efforts focused on updating the existing guidance to reflect the agency's current thinking or to address areas where additional clarity is needed would have a broader reach and address existing uncertainty in this area.

Specific recommendations pertaining to quality of submissions: (1)) adopt the use of an "assurance case" framework for 510(k) submissions, (2) submission of detailed photographs and schematics of the device under review and publish on the publicly available 510(k) database, (3) submitters keep one unit of the device available for CDRH to access during review of that device, as well as subsequent devices declaring that device as a predicate, (4) additional guidance and training for submitters and reviewers regarding the appropriate use of standards , (5) revise requirements for "declarations of conformity" with a standard to require providing summary testing to demonstrate conformity, and (6) revise 21 CFR 807.87 to require 510(k) submitters to provide a list and brief description of all scientific information known to or that should be reasonably known to the submitter.

Assurance case

At this time, we do not believe it is prudent to adopt the widespread use of a new framework, such as assurance case reports, for evaluating 510(k) submissions. Although used in other industries, assurance case reports are not typically used in the medical device industry. As such, extensive training of reviewers, managers, and industry would be necessary to implement such a widespread change.

As identified in the report, there is a certain level of lack of understanding of critical terms related to the concept of substantial equivalence, a concept in place for several decades. We believe efforts focused at addressing these areas both within the agency and the industry would better serve patients and the public health, than the implementation of an entirely new, untested framework.

Additionally, attempts to eliminate existing areas of misunderstanding may be stymied due to the simultaneous introduction of a new review framework, such as assurance case reports.

Detailed photographs and schematics

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

schematics is approached in a manner that does not compromise the competitiveness of the U.S. medical device industry, especially where public publication of detailed photographs or schematics will result in competitive harm to medical device companies.[8]

Keep device unit available for current and subsequent reviews
Increased use of vendor days, site visits, or face-to-face meetings with manufacturers for hands on access to devices are more appropriate means to educate staff on medical devices, than requiring manufacturers to keep each device indefinitely to aid CDRH in the review of future devices that may potentially rely on that device as a predicate.

This recommendation is logistically infeasible due to cost and space allocation. Storage of large capital equipment and devices with limited shelf life, such as IVD reagents, is simply impractical. Also, where several design iterations of a device have been cleared through several 510(k) submissions, retention of a sample of each would be impractical, especially for the previously cited device types.

Standards
We support the recommendation to provide to reviewers and industry additional guidance and training on the use of standards. Further, we encourage CDRH to expand its use of internationally, recognized standards from organizations such as ISO and IEC.

Scientific information known to or that should be reasonably known to the submitter
We recommend the agency reconsider the scope and application of this recommendation by focusing on a summary of technical and clinical information for a small, focused subset of higher risk class II devices for which uses and technologies are not well-characterized. Because the premarket process requires a demonstration of substantial information applying this requirement to all class II and class I devices subject to 510(k) clearance is excessive and suggestive of current PMA requirements. Additionally, the standard "should be reasonably known" is too vague to provide a consistent set of information.

Specific recommendations pertaining to type and level of evidence needed: (1) develop guidance defining a subset of class II devices called "class IIb," for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting would typically be necessary to support substantial equivalence. (2) training for reviewers and industry regarding the delineation between "class IIa" and "class IIb", (3) related to "class IIb" guidance provide greater clarity regarding the circumstances in which it will request clinical data in support of a 510(k), and what type and level of clinical data are adequate to support clearance, (4) define "clinical data" in guidance or through regulation, (5) seek greater authority to require postmarket surveillance studies as a condition of clearance for certain devices, (6) continue ongoing efforts to implement a UDI system and consider the possibility of using "real-world" data as part of a premarket submission for future 510(k)s, (7) guidance to provide greater clarity

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