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

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

FDA-2010-N-0348-0003

FDA-2010-N-0348-0004

FDA-2010-N-0348-0005

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

FDA-2010-N-0348-0006

Indiana Medical Device Manufacturers Council (IMDMC) (Danelle Miller) – 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 (William Vaughan) – Comment (posted 10/6/10)

FDA-2010-N-0348-0008

Thom Davis – Comment (Posted 10/6/10)

FDA-2010-N-0348-0009

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

FDA-2010-N-0348-0010

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

FDA-2010-N-0348-0011

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

FDA-2010-N-0348-0012

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

FDA-2010-N-0348-0013

BioMet –(Robert Durgin) Comment (posted 10/06/10)

FDA-2010-N-0348-0014

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

FDA-2010-N-0348-0015

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

FDA-2010-N-0348-0016

American Society for Radiology Oncology (ASTRO) (Laura Thevenot) – 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 (Amy McKinney) – Comment (posted 10/06/10)

FDA-2010-N-0348-0019

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

FDA-2010-N-0348-0020

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

FDA-2010-N-0348-0021

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

FDA-2010-N-0348-0022

American Association for Justice (AAJ) (C. Gibson Vance) – Comment (posted 10/06/10)

FDA-2010-N-0348-0023

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

FDA-2010-N-0348-0024

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

FDA-2010-N-0348-0025

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

FDA-2010-N-0348-0026

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

FDA-2010-N-0348-0027

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

FDA-2010-N-0348-0028

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

FDA-2010-N-0348-0029

Anonymous – Comment (posted 10/14/10)

FDA-2010-N-0348-0030

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

FDA-2010-N-0348-0031

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

FDA-2010-N-0348-0032

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

FDA-2010-N-0348-0033

Covidien (David Olson) – Comment (posted 10/14/10)

FDA-2010-N-0348-0034

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

FDA-2010-N-0348-0035

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

FDA-2010-N-0348-0036

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

FDA-2010-N-0348-00637

Medtronic, Inc (Susan Alpert) – 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

BIOCOM (Joe Panetta) – Comment (posted 10/14/10)

FDA-2010-N-0348-0041

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

FDA-2010-N-0348-0042

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

FDA-2010-N-0348-0043

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

FDA-2010-N-0348-0044

FDA-2010-N-0348-0046

California Healthcare Institute (CHI) (Todd Gillenwater) – Comment (posted 10/14/10)

FDA-2010-N-0348-0045

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

FDA-2010-N-0348-0047

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

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) (Marie Manteuffel) – Comment (posted 10/14/10)

FDA-2010-N-0348-0050

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

FDA-2010-N-0348-0051

CONNECT (Timothy Tardibono) – Comment (posted 10/14/10)

FDA-2010-N-0348-0052

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

FDA-2010-N-0348-0053

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

FDA-2010-N-0348-0054

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

FDA-2010-N-0348-0055

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

FDA-2010-N-0348-0056

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

FDA-2010-N-0348-0057

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

FDA-2010-N-0348-0058

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

FDA-2010-N-0348-0059

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

FDA-2010-N-0348-0060

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

FDA-2010-N-0348-0061

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

FDA-2010-N-0348-0062

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

FDA-2010-N-0348-0063

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

FDA-2010-N-0348-0064

American Association for Clinical Chemistry (AACC) (Catherine Hammett-Stabler) – Comment (posted 10/21/10)

FDA-2010-N-0348-0065

Zimmer, Inc. (Carol Vierling) – Comment (posted 11/02/10)

FDA-2010-N-0348-0066

MedTech (Heather Erickson) – Comment (posted 11/02/10)

FDA-2010-N-0348-0067

The Orthopedic Surgical Manufacturers Association (OSMA) (Susan Krasny) – Comment (posted 11/02/10)

FDA-2010-N-0348-0068

BIOCOM (Joe Panetta) – Comment (posted 11/02/10)

FDA-2010-N-0348-0069

SPS Medical Supply Corporation (Jennifer Griffin) – Comment (posted 11/02/10)

FDA-2010-N-0348-0070

LifeScience Alley (LSA) (Donald Gerhardt) – Comment (posted 11/02/10)

FDA-2010-N-0348-0071

Boston Scientific Corporation (Sheila Hemeon-Heyer) – Comment (posted 11/02/10)

FDA-2010-N-0348-0072

Best of Rowan, LLC (Steve Arey) – Comment (posted 11/03/10)

FDA-2010-N-0348-0073

The American College of Obstetricians and Gynecologists – Comment (posted 11/03/10)

FDA-2010-N-0348-0074

American Academy of Orthopaedic Surgeons, et al. (John Callaghan) – Comment (posted 11/09/10)

FDA-2010-N-0348-0075

Alliance of Specialty Medicine, et al. – Comment (posted 11/09/10)

FDA-2010-N-0348-0076

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

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 both of its stated goals. The result would be improved, science-based regulation; enhanced health and quality of life; and 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.

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 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 comments follow on the attached pages.

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
Director, Medical Industry Group
National Venture Capital Association
703-524-2549 (office)
703-405-5287 (cell)
kslone@nvca.org

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 namely 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 because of 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 labeled 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. In other cases, 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. In all of these cases,

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 Group proposal would eliminate or greatly reduce:

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, completely outside the control of the Sponsor need to take place to support the use. In both of these cases, forcing these uses 'on label' would simply shut down all innovation in the area.

In seeking in 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 too 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 uses 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.

While the *de* novo 510(k) process serves as an alternative mechanism for dealing with the new application of an existing technology to a novel 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 exceed 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 sates:

> 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 even worse trends relating to IDE approvals for the most novel and potentially important device submissions. It is likely that very long delays associated with just a few very novel submissions is 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 its 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 agree 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, 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 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, raise the risks in developing new technology. Frequent changes to precedent, or changes to trial design after a trial has begun, are enormously expensive and 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 therefore 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 kept, informed of major decisions by the Council, and could be 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.

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

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

Blake Jeffery, Executive Director
P.O. Box 441385, Indianapolis, IN 46244
Phone 317-951-1388 / Fax 317-974-1832
E-mail: IMDMCoffice ameritech.net / www.IMDMC.org

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

FDA-2010-N-0348-0008

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

---

[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

---

[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,

William Vaughan
Health Policy Analyst

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

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

AdvaMed
Advanced Medical Technology Association

September 21, 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"

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

---

[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.

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

FDA-2010-N-0348-0011

Kathryn Branca
SCC Soft Computer
5400 Tech Data Drive
Clearwater, FL 33760

September 22nd, 2010

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

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

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 Branca
Director of Quality Management
SCC Soft Computer

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

September 28, 2010

Division of Dockets Management (HFA-305)
Food & Drug Administration
5630 Fishers Lane
Room 1061
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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.	

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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"	

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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	

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.	

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

Section	Topic *Implementation*	Task Force on the Utilization of Science in Regulatory Decision Making Proposal	RTIB Response
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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

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.

11621 Research Circle • Alachua, FL 32615
Tel 386.418.8888 • 877.343.6832 • Fax 386.418.0342 • Customer Service 800.624.7238 • www.rtix.com

BioMet - Comment (posted 10/06/10)

FDA-2010-N-0348-0014

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

Mailing Address:
P.O. Box 587
Warsaw, IN 46581-0587
Toll Free: 800.348.9500
Office: 574.267 6639
Main Fax: 574.267 8137
www.biomet.com

Shipping Address:
56 East Bell Drive
Warsaw, IN 46582

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.

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

FDA-2010-N-0348-0015

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 – Comment (posted 10/06/10)

FDA-2010-N-0348-0016

BlueCross BlueShield Association

An Association of Independent Blue Cross and Blue Shield Plans

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

225 North Michigan Avenue
Chicago, Illinois 60601-7680
312.297.6840
Fax 312.297.5726
allan.korn@bcbsa.com

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

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

FDA-2010-N-0348-0017

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.

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.

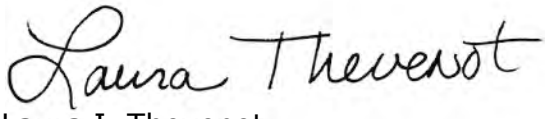
- ASTRO supports the working group recommendation that CDRH enhance its third-party reviewer training program and consider options for sharing more information about previous decisions with third-party reviewers to achieve greater consistency between in-house and third-party reviewers. ASTRO agrees that 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, Inc. – Comment (posted 10/6/10)

FDA-2010-N-0348-0018

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

5858 Horton Street, Suite 550 Emeryville CA 94608 T 510.420.6700 F 510.450.0675

3410 Industrial Blvd, Suite 103 West Sacramento, CA 95691 T 916.371.7974 F 916.669.0475

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.

5858 Horton Street, Suite 550 Emeryville CA 94608 T 510.420.6700 F 510.450.0675

3410 Industrial Blvd, Suite 103 West Sacramento, CA 95691 T 916.371.7974 F 916.669.0475

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

FDA-2010-N-0348-0019

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

4364 Round Lake Road
Arden Hills, MN 55112
Tel: 1.877.639.2796 (CRYO)
Fax: 1.877.510.7757
www.galilmedical.com

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.

<u>Discussion of Noted Errors</u>

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].

---

[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,

Amy E. McKinney

Amy E. McKinney
Director, Regulatory Affairs
Galil Medical Inc.

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

FDA-2010-N-0348-0020

Abbott Quality & Regulatory

April Veoukas
Strategic Regulatory Affairs
D-3QSA, AP6B
Telephone: (847) 937-8197

100 Abbott Park Road
Abbott Park, Illinois 60064-6091
Facsimile: (847) 935-0766
E-mail: april.veoukas@abbott.com

October 1, 2010

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

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]"

---

[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).

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

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

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

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

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

Clinical data

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

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

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

Postmarket surveillance as a condition of clearance

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

UDI

Abbott supports UDI for medical device labels based on the option of following GS1 or HIBCC standards implemented in a risk-based manner with an appropriate implementation time frame. We look forward to receiving a more detailed proposal in the form of a proposed rule subject to public notice and comment. It should be noted that submitters of 510(k)s may have limited or no access to device databases and electronic health record systems. We believe it is premature, at this time, to explore how data collected or associated with UDI may be used as part of the 510(k) process, and recommend CDRH defer evaluation of this option until such time as UDI is effective.

Manufacturing information

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

Pre-clearance inspection

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Clarify statutory listing requirements for submission of labeling

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

Electronic labeling repository

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

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

---

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

[14] 21 CFR 80731(e)

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

Transfers of 510(k) ownership

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

3. Continuous Quality Assurance

Recommendation: CDRH should enhance training, professional development, and knowledge-sharing among reviewers and managers, in order to support consistent, high-quality 510(k) reviews.

Specific recommendations pertaining to reviewer expertise and experience: (1) enhance recruitment, retention, training, and professional development of review staff, including providing opportunities for staff to stay abreast of recent scientific developments and new technologies and (2) establish a Center Science Council comprised of experienced reviewers and managers under the direction of the Deputy Center Director for Science to facilitate knowledge-sharing across review branches, divisions, and offices.

We support the agency's efforts to enhance recruitment, retention, training, and professional development of review staff, including providing opportunities for staff to stay abreast of recent scientific developments and new technologies, and offer the following suggestions:

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

We support the establishment of a Center Science Council comprised of experienced employees and managers under the direction of the Deputy Center Director for Science to provide oversight and help assure consistency across the Center.

The process and activity of the Council must be transparent to all stakeholders. Roles should be clearly defined for this group and made publicly available.

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

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

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

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

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

The implementation of periodic audits with the intent to drive greater knowledge and consistency among reviewers can improve the 510(k) program, if implemented in a manner that does not result in second-guessing of earlier decisions. Clearly defined objective audit criteria made publicly available will aid in the usefulness of the process. Any major lessons learned should be communicated to the industry in a timely manner with sufficient transition time to ensure that any changes in expectations during a pending submission do not result in significant delays. Finally, the agency needs to ensure that these audits do not lead to revisiting previous 510(k) decisions.

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

1. Enhancing CDRH's Scientific Knowledge Base

Recommendation: CDRH should take steps to improve its ability to readily access high-quality information about regulated products.

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

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

Least burdensome

Education and training of industry and staff on the substance and application of the least burdensome principles are appropriate steps. As noted in the report, the background of FDA's least burdensome guidance states, "[i]n order for the least burdensome approach to be successful, it is important that industry continue to meet all of its statutory and regulatory obligations, including preparation of appropriate scientifically sound data to support premarket submissions.[15]" The report further notes, "[t]hese principles are consistent with good governance in general.[16]" Rather than begin with revision of the guidance, we recommend the agency concentrate its efforts on education and training of industry and staff on the principles of least burdensome. The guidance document issued in October of 2002 implemented provisions of FDAMA 1997 approximately five years after its enactment. It was issued as a draft subject to notice and comment, and then re-issued as a final guidance after consideration of the comments received. Continued education and training are a necessary step to ensure adequate understanding and application of the least burdensome principles. This approach should be implemented and evaluated before any changes in current guidance are proposed.

Clinical trials

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

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

---

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

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

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

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

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

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

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

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

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

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

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

Specific recommendations pertain to: (1) conduct an assessment of staffing needs to accomplish mission-critical functions, (2) determine staff needed to accommodate anticipated future scientific challenges, (3) enhance employee training and professional development for optimal staff performance, (4) consider making greater use of site visits and other means of engagement with outside experts in a variety of areas, including clinical care, (5) develop more effective mechanisms for cataloging CDRH's internal expertise, assess the effectiveness of the inter-Office/Center consult process, and enhance the infrastructure and tools used to provide meaningful up-to-date information about a device or group of devices to Center staff.

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

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

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

Specific recommendations pertain to: (1) develop a web-based network of external experts, using social media to leverage external expertise related to novel technologies and scientific questions and (2) assess best-practices for staff engagement with external experts and develop standard business processes for the appropriate use of external experts to assure consistency and address potential bias, and (3) explore site visits, including clinical care, interaction at the employee level, and collaborative relationships with other science-led organizations.

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

As previously noted, we support the agency's efforts to enhance recruitment, retention, training, and professional development of review staff, including providing opportunities for staff to stay abreast of recent scientific developments and new technologies, and offer the following suggestions:

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

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

Recommendation: CDRH should establish and adhere to as predictable an approach as practical for determining what action, if any, is warranted with respect to a particular product or group of products on the basis of new scientific information.

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

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

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

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

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

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

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

3. Promptly Communicating Current or Evolving Thinking to All Affected Parties

Recommendation: CDRH should make use of more rapid communication tools to convey its current thinking and expectations.

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

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

Guidance

We support the development of additional product specific guidance and training for FDA staff and industry. Increased issuance of Level 1 guidance immediately in effect raises concerns about implementation of new expectations without adequate notice to affected stakeholders, which is a challenge for product and submission development. At any one time, there will be products in various stages of development, including submissions pending before the agency, applications ready for submission to the agency, or existing device clinical trials near completion. There is a real need for notice and comment on guidance documents, and therefore the use of Level 1 guidance immediately in effect is best reserved to only those places where there is an immediate public health issue.

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

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

Notice to the Industry

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

We recommend the agency clearly define in a transparent manner the types of information and circumstances in which it would be appropriate to issue a NTI. Use of NTIs to communicate changes in thinking related to product specific issues impacting safety or effectiveness has the potential to improve the current process, where currently such issues may be communicated on a one to one basis. Overuse of NTIs to communicate procedural topics, such as application format, or other topics which can be addressed via Level 2 guidance will minimize the effectiveness of the NTIs and cause unnecessary complexity to the process. Clearly defining the types of content to communicate via NTIs will maximize the utility and effectiveness of NTIs.

A critical aspect of the NTI proposal is recognition that at any one time when the agency issues a NTI, there will be products in various stages of development, including submissions pending before the agency, applications ready for submission to the agency, or existing device clinical trials near completion. Because of these dynamics it is important that the NTI standard practice include a mechanism for phasing in the new expectations. As with current practice, issuance of a final guidance sets forth the agency's current thinking, but recognizes that other mechanisms may exist for addressing the particular topic. Thus, a company may be able to address the subject of the NTI in another manner, and the standard practice for NTIs should continue to allow for this.

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

We agree with the recommendation of providing the letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations. In addition, we encourage the agency to use additional communication tools to industry, so that companies contemplating the design, development and commercialization of a particular class of devices have knowledge of the change in agency thinking. Specifically, we recommend posting on the CDRH website NTIs in a readily accessible manner and tagging NTIs for inclusion in the CDRH email, "What's New at CDRH Update."

Further, a webpage dedicated to topics related to new science is certainly an important step to increasing transparency and understanding. Inclusion and consolidation of the NTIs on this page along with the standard operating procedure that governs NTI development is recommended. We recommend constructing the web page in a manner that is readily accessible, consolidates all new science information in one location, and minimizes the use of multiple links to obtain this information.

Lastly, we believe adoption of a standard process for creating and issuing NTIs should not preclude the agency from communicating anticipated changes in thinking at pre-IDE meetings or other pre-submission meetings if the NTI is still under review within the agency. One can envision a situation where a company leaves a pre-IDE meeting with an understanding of a path forward, only to receive a NTI shortly after the meeting. Steps to avoid such situations will benefit the agency and its stakeholders.

Electronic labeling repository

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

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

Recommendation: CDRH should provide additional information to its external constituencies about its process for determining an appropriate response to new science and the bases for its actions.

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

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

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

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

Sincerely,

April Veoukas, J.D.
Director, Regulatory Affairs
Abbott Quality & Regulatory
Abbott Laboratories

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

[FDA-2010-N-0348]

Oct. 4, 2010

Dir Sir,
Center for Devices and Radiological Health
U.S Food and Drug Administration,

Hiroshi Ishikawa
Chairman of International Division
Japan Industries Association of Radiological Systems(JIRA)
SUMITOMO FUDOSAN IIDABASHI BLDG., No.2
2-2-23, KOURAKU, BUNKYO-KU,
TOKYO,112-0004 JAPAN
PHONE:81-3-3816-3450
FAX:81-3-3818-8920
URL:http//www.jira-net.or.jp
Contact:
Mitsuro Tokugawa
Secretariat
JIRA

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

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

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

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

JIRA's opinion is described briefly as follows.

1) About the new establishment of class IIb

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

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

2) About minor modifications

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

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

3) Submission of a summary of scientific information regarding

the safety and/or effectiveness

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

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

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

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

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

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

FDA-2010-N-0348-0023

October 4, 2010

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

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

Dear Sir or Madam:

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

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

I. Complex Devices Deserve Increased Scrutiny

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

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

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

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

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

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

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

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

---

[2] *Id.*

[3] *Id.*

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

B. The FDA Should Require Post-Market Surveillance Studies

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

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

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

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

Sincerely,

C. Gibson Vance, President
American Association for Justice

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

[6] *Id.*

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

FDA-2010-N-0348-0024

Roche

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

4 October 2010

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

Dear Sir/Madam,

Roche Diagnostics ("Roche") respectfully submits the following comments on the Center for Devices and Radiological Health ("CDRH") *510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations.* Roche appreciates the tremendous effort that CDRH has undertaken in assessing the strengths and limitations of the 510(k) program, and commends CDRH for focusing on the program's dual aims: (1) To assure, through a quality review process, that marketed devices, subject to general and applicable special controls, provide a reasonable assurance of safety and effectiveness; and (2) to foster innovation. Roche understands the difficulty in balancing these two aims, and is pleased that CDRH has been able to strike this balance with some of its proposed improvements.

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

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

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

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

Intended Use and Indication

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

Off-Label Use

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

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

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

Split and Multiple Predicates

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

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

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

---

[2] Section 513(i)(1)(e)(i) of the Act provides that "[a]ny determination by the Secretary of the intended use of a device shall be based upon the proposed labeling submitted in a report for the device under section 510(k). However, when determining that a device can be found substantially equivalent to a legally marketed device, the director of the organizational unit responsible for regulating devices (in this subparagraph referred to as the "Director") may require a statement in labeling that provides appropriate information regarding a use of the device not identified in the proposed labeling if, after providing an opportunity for consultation with the person who submitted such report, the Director determines and states in writing – (I) that there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device; and (II) that such use could cause harm." 21 U.S.C. § 360c(i)(1)(e)(i).

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

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

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

Class IIb Subset

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

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

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

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

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

Rescission

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

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

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

[4] 21 U.S.C. § 360c.

Roche

General Comments

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

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

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

Respectfully yours,

Roche Diagnostics

Danelle R. Miller
Legal Counsel Global Quality
and Regulatory Affairs

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

FDA-2010-N-0348-0025

www.lilly.com

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
U.S.A.

Phone 317 276 2000

October 04, 2010

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

Re: Docket No. FDA-2010-N-0348,
CDRH 510(k) Working Group Preliminary Report and Recommendations

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

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

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

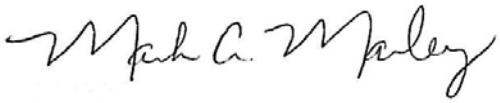
The report clearly establishes that FDA s current training of its staff is ineffective in many respects, and that many of its guidance documents are not sufficiently clear. Unless these root causes of shortcomings in the 510(k) process are addressed, no change to the program can achieve meaningful improvement.

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

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

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

Sincerely,



Mark A. Marley
Eli Lilly and Company
Regulatory Affairs

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

Formation of Class IIb:

"CDRH should take steps through guidance and regulation to facilitate the efficient submission of high-quality 510(k) device information, in part by better clarifying and more effectively communicating its evidentiary expectations through the creation, via guidance, of a new "class IIb" device subset." [CDRH 510(k) Working Group Preliminary Report and Recommendations, Volume I, Recommendation 5.2.1]

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

Lilly Comments:

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

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

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

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

Substantial Equivalence

"The 510(k) Working Group recommends that CDRH revise existing guidance to consolidate the concepts of "indication for use" and "intended use" into a single term, "intended use," in order to reduce inconsistencies in their interpretation and application." [CDRH Volume I, Section 1.1, p.7]

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

"…explore the possibility of pursuing a statutory amendment … that would provide the agency with express authority to consider an off-label use, in certain limited circumstances, when determining the "intended use" of a device under review through the 510(k) process." [CDRH Volume I, Section 1.1, p.8]

"The 510(k) Working Group recommends that CDRH develop guidance on the appropriate use of more than one predicate, explaining when "multiple predicates" may be used. The Center should also explore the possibility of explicitly disallowing the use of "split predicates." [CDRH Volume I, Section 1.1, p. 9]

Lilly Comments:

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

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

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

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

Disallowing the use of "split predicates" for a given device under 510(k) review could result in an unnecessary burden on the PMA and *de novo* submission programs for both CDRH and industry. For this reason and those described below, we respectfully disagree with these CDRH recommendations.

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

Unreported Device Modifications

"The 510(k) Working Group recommends that CDR H revise existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k), and, for those modifications that do warrant a new 510(k), what modifications are eligible for a Special 510(k)." [CDRH Volume I, Section 5.2.1.1]

"The 510(k) Working Group further recommends that CDRH explore the feasibility of requiring each manufacturer to provide regular, periodic updates to the Center listing any modifications made to its device without the submission of a new 510(k), and clearly explaining why each modification noted did not warrant a new 510(k). The Center could consider phasing in this requirement, applying it initially to the "class IIb" device subset described in Section 5.2.1.3, below, for example, and expanding it to a larger set of devices over time." [CDRH Volume I, Section 1.1]

Lilly Comments:

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

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

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

Quality of Submissions

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

"The 510(k) Working Group further recommends that CDRH explore the possibility of requiring each 510(k) submitter to provide as part of its 510(k) detailed photographs and schematics of the device under review, in order allow review staff to develop a better understanding of the device's key features." [CDRH Volume I, Section1.1, p. 10]

"The 510(k) Working Group recommends that CDRH consider revising 21 CFR 807.87, to explicitly require 510(k) submitters to provide a list and brief description of all scientific information regarding

the safety and/or effectiveness of a new device known to or that should be reasonably known to the submitter." [CDRH Volume I, Section1.1, p.11]

"The 510(k) Working Group recommends that CDRH revise existing regulations to clarify the statutory listing requirements for the submission of labeling. CDRH should also explore the feasibility of requiring manufacturers to electronically submit final device labeling to FDA by the time of clearance or within a reasonable period of time after clearance, and also to provide regular, periodic updates to device labeling, potentially as part of annual registration and listing or through another structured electronic collection mechanism." [CDRH Volume I, Section1.1, p.13-14]

Lilly Comments:

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

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

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

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

Unique Device Identification

"The 510(k) Working Group further recommends that CDRH continue its ongoing effort to implement a unique device identification (UDI) system and consider, as part of this effort, the possibility of using "real-world" data (e.g., anonymized data on device use and outcomes pooled from electronic health record systems) as part of a premarket submission for future 510(k)s."[CDRH Volume I, Section5.2.1.3, p.79]

Lilly Comments:

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

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

Please see attached comment letter

FDA-2010-N-0348-0026

novo nordisk®

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

September 29, 2010

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

RE: Docket No. 2010-N-0348

CDRH 510(k) Working Group Preliminary Report and Recommendations

Dear Sir/Madam:

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

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

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

Intended use to support substantial equivalence

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

Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540
609-987-5800
www.novonordisk-us.com

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

Concerns about predicate quality

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

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

Split predicates and multiple predicates

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

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

Quality of submissions

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

Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540
609-987-5800 phone
www.novonordisk-us.com

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

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

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

Product codes

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

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

Class IIb device subset

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

Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540
609-987-5800 phone
www.novonordisk-us.com

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

Third-party review

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

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

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

Sincerely,

Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
Novo Nordisk Inc.

Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540
609-987-5800 phone
www.novonordisk-us.com

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

October 4, 2010

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

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

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

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

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

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

Blake Jeffery, Executive Director
P.O. Box 441385, Indianapolis, IN 46244
Phone 317-951-1388 / Fax 317-974-1832
E-mail: IMDMCoffice ameritech.net / www.IMDMC.org

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

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

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

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

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

De Novo Classification

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

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

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

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

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

Off-Label Use

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

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

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

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

---

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

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

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

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

Condition of Approval Studies

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

Comment: Although IMDMC supports the appropriate use of postmarket studies for specified higher risk devices, we do not support the recommendation to potentially seek greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices. In light of the existing authority to include postmarket studies in premarket special controls and through section 522, further authority is unnecessary. It also seems that FDA would need formal regulatory or statutory authority to make any such change.

Definition of Substantial Equivalence

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

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

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

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

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

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

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

Assurance Case

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

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

Periodic Reporting Requirements – All 510(k) Device Modifications

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

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

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

Formation of Class IIb

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

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

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

Blake Jeffery, Executive Director
P.O. Box 441385, Indianapolis, IN 46244
Phone 317-951-1388 / Fax 317-974-1832
E-mail: IMDMCoffice ameritech.net / www.IMDMC.org

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

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

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

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

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

[4] Guidance for Cardiovascular Intravascular Filter 510(k) Submissions; issued November 26, 1999

Class II Special Controls Guidance Document: Root-form Endosseous Dental Implants and Endosseous Dental Implant Abutments; issued May 12, 2004

Blake Jeffery, Executive Director
P.O. Box 441385, Indianapolis, IN 46244
Phone 317-951-1388 / Fax 317-974-1832
E-mail: IMDMCoffice ameritech.net / www.IMDMC.org

Essential Requirement for Summaries

Lack of Clarity (in submissions) – Detailed Photos, Schematics, and Samples
Proposal: The 510(k) Working Group further recommends that CDRH explore the possibility of requiring each 510(k) submitter to provide as part of its 510(k) detailed photographs and schematics of the device under review, in order allow review staff to develop a better understanding of the device's key features. Currently, CDRH receives photographs or schematics as part of most 510(k)s; however, receiving both as a general matter would provide review staff with more thorough information without significant additional burden to submitters. Further, CDRH could include photographs and schematics, to the extent that they do not contain proprietary information, as part of its enhanced public 510(k) database, described below, to allow prospective 510(k) submitters to develop a more accurate understanding of potential predicates. Exceptions could be made for cases in which a photograph or schematic of the device under review will not provide additional useful information, as in the case of software-only devices. CDRH should also explore the possibility of requiring each 510(k) submitter to keep at least one unit of the device under review available for CDRH to access upon request, so that review staff could, as needed, examine the device hands-on as part of the review of the device itself, or during future reviews in which the device in question is cited as a predicate.

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

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

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

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

Blake Jeffery, Executive Director
P.O. Box 441385, Indianapolis, IN 46244
Phone 317-951-1388 / Fax 317-974-1832
E-mail: IMDMCoffice ameritech.net / www.IMDMC.org

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

Use of "Split Predicates" and "Multiple Predicates"

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

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

Disallowing the use of "split predicates" and / or more than five predicates for a given device under 510(k) review could result in an unnecessary burden on the PMA and *de novo* submission programs for both CDRH and industry. For this reason and those described below, IMDMC respectfully disagrees with these CDRH recommendations.

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

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

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

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

Sincerely,

Danelle R. Miller
President

Blake Jeffery, Executive Director
P.O. Box 441385, Indianapolis, IN 46244

Phone 317-951-1388 / Fax 317-974-1832
E-mail: IMDMCoffice ameritech.net / www.IMDMC.org

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

FDA-2010-N-0348-0029

715 Albany St. TW1
Boston, MA 02118

DOCKET NO. FDA – 2010 – N- 0348

October 4, 2010

Dr. Jeffrey Shuren
Director
Center for Devices and Radiological Health
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO66-5429
Silver Spring, MD 20993

Dear Dr. Shuren:

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

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

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

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

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

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

Sincerely,

Thomas J. Sommer
President

DOCKET NO. FDA- 2010 – N - 0348

MassMEDIC Comments on Proposed 510(k) Revisions September 2010

VOLUME I – CDRH Preliminary Internal Evaluations

510(k) Working Group

Use of "Split Predicates" and "Multiple Predicates"

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

MassMEDIC Comment

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

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

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

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

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

Type and Level of Evidence Needed

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

MassMEDIC Comment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Unreported Device Modifications

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

MassMEDIC Comment

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

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

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

"Same Intended Use"

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

MassMEDIC Comment

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

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

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

"Different Questions of Safety and Effectiveness"

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

MassMEDIC Comment

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

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

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

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

Predicate Device Concerns

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

MassMEDIC Comment

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

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

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

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

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

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

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

VOLUME II – CDRH Preliminary Internal Evaluations

Task Force on the Utilization of Science in Regulatory Decision Making

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

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

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

Leveraging External Scientific Expertise

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

Promoting Flexible Staffing Policies to Alleviate Peak Workload Demands

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

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