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Advanced Medical Technology Association

October 4, 2010

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

RE: Docket No. FDA-2010-N-0348: 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 Advanced Medical Technology Association ("AdvaMed") is pleased to provide the enclosed comments and recommendations on the Center for Devices and Radiological Health *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.*

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. Our members produce nearly 60 percent of the health care technology purchased annually in the United States. These members range from the smallest to the largest medical technology innovators and companies. Nearly 70 percent of our members have less than $30 million in sales annually.

AdvaMed appreciates the opportunity to comment.

Sincerely,

Janet Trunzo
Executive Vice President
Technology and Regulatory Affairs

AdvaMed
Advanced Medical Technology Association

Comments and Recommendations on
Center for Devices and Radiological Health
510(K) Working Group Preliminary Report and Recommendations
Task Force On The Utilization of Science in Regulatory Decision Making
Docket No. FDA-2010-N-0348

Submitted by:
Advanced Medical Technology Association (AdvaMed)

October 4, 2010

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ATTACHMENTS

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General Comments

AdvaMed commends the 510(k) Working Group (the Working Group) and the Task Force on the Utilization of Science in Regulatory Decision Making (the Task Force) on their thorough review and evaluation of the 510(k) program and the use of science. AdvaMed supports the Working Group's stated goals of the 510(k) program to "(1) 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) "fostering innovation in the medical device industry" and the Task Force's stated goal of making recommendations to CDRH "on how the Center can quickly incorporate new science – including evolving information, novel technologies, and new scientific methods – into its decision making, while also maintaining as much predictability as practical."

AdvaMed also supports many of the concepts outlined in the proposals or elements of the proposals (contingent upon their appropriate implementation under existing statutory authority) contained in the two reports (see our more detailed specific comments below) that we believe will enhance and improve program predictability. These include among others: improving the training and education of reviewers; streamlining the implementation of the *de novo* classification process; establishing collaborative relationships to better leverage external scientific expertise; establishing a Center Science Council to provide oversight and consistency across reviews; posting of reviewer decision summaries and a webpage for new information; a standard template for 510(k) summaries; and documentation of 510(k) ownership transfer.

Nonetheless, we are concerned that the cumulative effect of the multiple CDRH proposals in the two reports would result in a revolutionary change in both the 510(k) process and in the larger regulatory framework and may adversely affect the ability of CDRH to effectively carry out mission-critical functions, including timely reviews. Wholesale changes to the program will also impact industry's ability to efficiently bring new devices to market.

AdvaMed believes proposed changes to the program must also be considered within two important parameters. First, the program as a whole has an admirable safety record. Recent, independent studies by Dr. William Maisel of the Medical Device Safety Institute at the Beth Israel Deaconess Medical Center, Professor Ralph Hall of the University of Minnesota, and Battelle Memorial Institute all show an extremely low rate of recall of medical devices and diagnostics because of safety problems. The Battelle Memorial Institute report is provided in Attachment A.

Second, as documented in the body of the report, there has been a significant deterioration in the efficiency and consistency of the 510(k) review process. If these trends are not reversed, there will be a long-term negative impact on patient access to new and improved treatments and to investment by and in device companies and others in the development of new products. Key statistics demonstrating these points include:[1]

[1] Statistics derived from ODE Annual Performance Reports and FDA's 510(k) report (page 39).

- The average total 510(k) decision time has risen 20 percent (97 days in 2002 vs. 116 days in 2008)
- The number of days 510(k) submitters spend answering FDA requests for more data has nearly tripled (19 days in 2002 vs. 51 days in 2008)
- The number of review cycles (the number of times FDA "stops the clock" on its review because it has decided to ask the manufacturer for more information) per 510(k) application increased by one-third between 2002 and 2008 (1.4 per application in 2002 vs. 1.9 in 2008)
- The percentage of 510(k)s withdrawn by sponsors has skyrocketed 89 percent from 2004 to 2009 (nine percent to 17 percent).

Importantly, the 510(k) report establishes that review staff fails to consistently interpret regulatory requirements. This suggests that there may be two over-arching root causes leading to inconsistent interpretations: (1) review staff may not be effectively trained; and (2) the guidances they follow are not sufficiently clear. Changes to the existing system will not constitute an improvement unless these root causes are first addressed. CDRH should consider whether improved training, clearer guidances, and guidance development would eliminate the need for some of the proposed changes to the program.

We also urge CDRH to establish clear program metrics. Although the 510(k) and science program reviews were thorough, without established program metrics, some of the proposed changes may be intended to correct problems based on a few outliers or anecdotes when resources could be better targeted elsewhere.

Once the impact of improved training and improved guidance has been assessed, and clear program metrics have been established, AdvaMed recommends that CDRH prioritize and implement a limited number of selected recommendations on which there is general agreement. Once these have been implemented, additional recommendations on which there is agreement can be launched and implemented. A process that tries to implement too many changes at once would overwhelm CDRH, its reviewers and industry, and likely will not lead to improvement. AdvaMed has specific recommendations for those proposals that should be implemented on a priority basis:

- Establishment of a Center Science Council to ensure consistency and predictability in conjunction with metrics to assess whether the new process is effective.
- Revision of the existing guidance to streamline the implementation of the *de novo* classification process and to clarify evidentiary expectations for *de novo* requests.

The table below also outlines at-a-glance the AdvaMed position on each of the 510(k) Working Group and Utilization of Science in Regulatory Decision-making recommendations and sub-proposals within the recommendations. In each case, we have stated whether AdvaMed "supports," "supports with modifications," or "does not support" the recommendation and the basis for our position. Below, please find our specific comments on each of the CDRH recommendations.

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SUMMARY OF ADVAMED POSITIONS ON WORKING GROUP/TASK FORCE RECOMMENDATIONS

CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
510(k) Report			
The 510(k) Working Group recommends that CDRH revise existing guidance to consolidate the concepts of "indication for use" and "intended use" into a single term, "intended use," in order to reduce inconsistencies in their interpretation and application. Several public comments expressed concern that, if these two terms were combined, any proposed change in a device's label indications could be considered a change in "intended use." The Working Group recognizes the importance of providing submitters with the flexibility to propose certain changes to their labeling, without such a change necessarily constituting a new "intended use." Therefore it recommends that CDRH carefully consider what characteristics should be included under the term "intended use," so that modifications that are currently considered to be only changes in "indications for use" and that CDRH determines do not constitute a new "intended use," are not in the future necessarily construed as changes in "intended use" merely because of a change in semantics. Any change in terminology would be intended to provide greater clarity and simplicity, not necessarily to make the concept of "intended use" more restrictive.		✓ Revise existing guidance to *clarify* each term, *not consolidate* terms.	✓
The Center should also carefully consider what it should call the existing "Indications for Use" statement in device labeling and the "Indications for Use" form currently required for all 510(k)s, in order to avoid confusion in terminology but still maintain an appropriate level of flexibility for submitters.		✓ Include indications for use in *labeling* but not *label.*	
The 510(k) Working Group recommends that CDRH develop or revise existing guidance to clearly identify the characteristics that should be included in the concept of "intended use."		✓ Revise existing guidance to *clarify* each term, *not consolidate* terms.	
The 510(k) Working Group further recommends that CDRH provide training for reviewers and managers on how to determine "intended use." Such training should clarify the elements of a device application that should be considered when determining the "intended use," e.g., product labeling, device design (explicit or implied), literature, and existing preclinical or clinical data. Training on "intended use" should also be provided to industry.		✓ Reviewers should be trained on how to determine *each* term.	
The 510(k) Working Group recommends that CDRH explore the possibility of pursuing a statutory amendment to section 513(i)(1)(E) of the Federal, Food, Drug and Cosmetic Act ... that would provide the agency with the express authority to consider an off-label use, in			✓

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
certain limited circumstances, when determining the "intended use" of a device under review through the 510(k) process.			
The 510(k) Working Group recommends that CDRH reconcile the language in its 510(k) flowchart (shown on page 27 of this report) with the language provided in section 513(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360c(i) regarding "different technological characteristics" and "different questions of safety and efficacy."			✓
The 510(k) Working Group recommends that CDRH revise existing guidance to provide clear criteria for identifying "different questions of safety and effectiveness" and to identify a core list of technological changes that generally raise such questions (e.g., a change in energy source, a different fundamental scientific technology).		✓ Identifying "new types of safety and effectiveness questions"	
The 510(k) Working Group further recommends that CDRH develop and provide training for reviewers and managers on how to determine whether a 510(k) raises "different questions of safety and effectiveness." Training on "different technological characteristics" and "different questions of safety and effectiveness" should also be provided to industry.		✓ Identifying "new types of safety and effectiveness questions"	
The 510(k) Working Group recommends that CDRH consider developing guidance on when a device should no longer be available for use as a predicate because of safety and/or effectiveness concerns. It is expected that such a finding would be an uncommon occurrence. Any factors set forth in guidance regarding when a device should no longer be used as a predicate should be well-reasoned, well-supported, and established with input from a range of stakeholders, and unintended consequences should be carefully considered.			✓
The 510(k) Working Group recommends that CDRH consider issuing a regulation to define the scope, grounds, and appropriate procedures, including notice and an opportunity for a hearing, for the exercise of its authority to fully or partially rescind a 510(k) clearance. As part of this process, the Center should also consider whether additional authority is needed.			✓
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.		✓ Support guidance on use of multiples with no limitation on the number allowed.	
The Center should also explore the possibility of explicitly disallowing the use of "split predicates."			✓
In addition, CDRH should update its existing bundling guidance to clarify the distinction between multi-parameter or multiplex devices (described in Section 5.1.2.3 of this report) and bundled submissions (described in Section 4.3.4.2).		✓ Only to clarify the distinction between multi-parameter or	

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
		multiplex devices	
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.	✓		
The 510(k) Working Group further recommends that CDRH conduct additional analyses to determine the basis for the apparent association between citing more than five predicates and a greater mean rate of adverse event reports, as shown in Section 5.1.2.3 of this report.			✓
The 510(k) Working Group recommends that CDRH revise existing guidance to streamline the current implementation of the de novo classification process and clarify its evidentiary expectations for de novo requests. The Center should encourage pre-submission engagement between submitters and review staff to discuss the appropriate information to provide to CDRH for devices eligible for de novo classification, potentially in lieu of an exhaustive 510(k) review. The Center should also consider exploring the possibility of establishing a generic set of controls that could serve as baseline special controls for devices classified into class II through the de novo process, and which could be augmented with additional device-specific special controls as needed.	✓		
The 510(k) Working Group recommends that CDRH revise existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k), and, for those modifications that do warrant a new 510(k), what modifications are eligible for a Special 510(k).	✓		
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.			✓
The 510(k) Working Group recommends that CDRH consider adopting the use of an "assurance case" framework for 510(k) submissions. An "assurance case" is a formal method for demonstrating the validity of a claim by providing a convincing argument together with supporting evidence. It is a way to structure arguments to help ensure that top-level claims are credible and supported. If CDRH pursues this approach, the Center should develop guidance on how submitters should develop and use an assurance case to			✓

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
make adequate, structured, and well-supported predicate comparisons in their 510(k)s. The guidance should include the expectation that all device description and intended use information should be submitted and described in detail in a single section of a 510(k). The guidance should also clearly reiterate the long-standing expectation that 510(k)s should describe any modifications made to a device since its previous clearance. CDRH should also develop training for reviewers and managers on how to evaluate assurance cases.			
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.			✓ Request, not require, photographs and graphic depictions.
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.			✓ Request, not require unit of device.
The 510(k) Working Group recommends that CDRH provide additional guidance and training for submitters and review staff regarding the appropriate use of consensus standards, including proper documentation with a 510(k).	✓		
CDRH should also consider revising the requirements for "declaration of conformity" with a standard, for example by requiring submitters to provide a summary of testing to demonstrate conformity, if they choose to make use of a "declaration of conformity."			✓
The 510(k) Working Group recommends that CDRH should 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.			✓
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			✓ (See AdvaMed proposal for

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
necessary to support a substantial equivalence determination.			subset of Class II.)
The 510(k) Working Group further recommends that CDRH develop and implement training for review staff and industry regarding the delineation between "class IIa" and "class IIb."			✓
The 510(k) Working Group recommends that CDRH, as part of the "class IIb" guidance described above, provide greater clarity regarding the circumstances in which it will request clinical data in support of a 510(k), and what type and level of clinical data are adequate to support clearance. CDRH should, within this guidance or through regulation, define the term "clinical data" to foster a common understanding among review staff and submitters about types of information that may constitute "clinical data." General recommendations related to the least burdensome provisions, premarket data quality, clinical study design, and CDRH's mechanisms for pre-submission interactions, including the pre-IDE and IDE processes, are discussed further in the preliminary report of the Center's Task Force on the Utilization of Science in Regulatory Decision Making (described further in Section 2, below). That report also recommends steps CDRH should take to make well-informed, consistent decisions, including steps to make better use of external experts.		✓ Support greater clarity of circumstances and definition of clinical data. Do not support "Class IIb" category. All IVD's should not be placed in "Class IIb."	
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.		✓ Support exploring *current* authority	✓ Do not support *expanding* postmarket authority
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.		✓ Premature to consider submission of data from electronic records.	
The 510(k) Working Group recommends that CDRH develop guidance to provide greater clarity regarding what situations may warrant the submission of manufacturing process information as part of a 510(k), and include a discussion of such information as part of its "class IIb" guidance.		✓ Should apply to only a small subset; should be summary information only; should not include IVD products.	
The 510(k) Working Group further recommends that CDRH clarify when it is appropriate to use its authority to withhold clearance on the basis of a failure to comply with good manufacturing requirements in situations where there is a substantial likelihood that such failure will potentially present a serious risk to human health . . .		✓ Clarify when it is appropriate to use its current authority and incorporate due process with manufacturer's input.	

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
. . . and include a discussion of pre-clearance inspections as part of its "class IIb" guidance.			✓ Do not support preclearance inspections.
The 510(k) Working Group recommends that CDRH develop guidance and Standard Operating Procedures (SOPs) on the development and assignment of product codes, in order to standardize these processes and to better address the information management needs of the Center's staff and external constituencies.	✓		
510(k) Working Group further recommends that CDRH enhance existing staff training on the development and assignment of product codes.	✓		
The 510(k) Working Group recommends that CDRH develop a publicly available, easily searchable database that includes, for each cleared device, a verified 510(k) summary, photographs and schematics of the device, to the extent that they do not contain proprietary information, and information showing how cleared 510(k)s relate to each other and identifying the premarket submission that provided the original data or validation for a particular product type.		✓ Photographs and schematics should not be included in the public database.	
The 510(k) Working Group recommends that CDRH develop guidance and SOPs for the development of 510(k) summaries to assure they are accurate and include all required information identified in 21 CFR 807.92. The Center should consider developing a standardized electronic template for 510(k) summaries.	✓		
The 510(k) Working Group recommends that CDRH revise existing regulations to clarify the statutory listing requirements for submission of labeling. CDRH should also explore the feasibility of requiring manufacturers to electronically submit final device labeling to FDA by the time of clearance or within a reasonable period of time after clearance, and also to provide regular, periodic updates to device labeling, potentially as part of annual registration and listing or through another structured electronic collection mechanism. If CDRH adopts this approach, updated labeling should be posted as promptly as feasible on the Center's public 510(k) database after such labeling has been screened by Center staff to check for consistency with the device clearance. In exploring this approach, CDRH should consider options to assure that labeling could be screened efficiently, without placing a significant additional burden on review staff. For example, to allow for more rapid review of labeling changes, the Center could consider the feasibility of requiring manufacturers to submit a clean copy and a redlined copy of final labeling and subsequent updates, highlighting any revisions made since the previous iteration. As a longer-term effort, the Center could explore greater use of software tools to facilitate rapid screening of labeling changes. The Center should consider phasing in this requirement, potentially starting with only a subset of devices, such as the "class IIb" device subset described above, or with a particular section			✓

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
of labeling. CDRH should also consider posting on its public 510(k) database the version of the labeling cleared with each submission as "preliminary labeling," in order to provide this information even before the Center has received and screened final labeling.			
The 510(k) Working Group recommends that CDRH develop guidance and regulations regarding appropriate documentation of transfers of 510(k) ownership. The Center should update its 510(k) database in a timely manner when a transfer of ownership occurs.	✓		
The 510(k) Working Group recommends that CDRH continue to take steps to enhance recruitment, retention, training, and professional development of review staff, including providing opportunities for staff to stay abreast of recent scientific developments and new technologies. This should include increased engagement with outside experts, as discussed further in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making (described further in Section 2, below).	✓		
The 510(k) Working Group further recommends that CDRH consider establishing a Center Science Council comprised of experienced reviewers and managers and under the direction of the Deputy Center Director for Science. The Science Council should serve as a cross-cutting oversight body that can facilitate knowledge-sharing across review branches, divisions, and offices, consistent with CDRH's other ongoing efforts to improve internal communication and integration. The Science Council's role in improving the consistency of Center decisions is discussed in greater detail in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making.		✓	
The 510(k) Working Group recommends that CDRH develop a process for regularly evaluating the list of device types eligible for third-party review and adding or removing device types as appropriate based on available information. 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.			✓
The 510(k) Working Group further recommends CDRH enhance its third-party reviewer training program and consider options for sharing more information about previous decisions with third-party reviewers, in order to assure greater consistency between in-house and third-party reviews.	✓		
The 510(k) Working Group recommends that CDRH develop metrics to continuously assess the quality, consistency, and effectiveness of the 510(k) program, and also to measure the effect of any actions taken to improve the program. As part of this effort, the Center should consider how to make optimal use of existing internal data sources to help evaluate 510(k) program performance.	✓		
The 510(k) Working Group further recommends that CDRH 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		✓ Define objective of audit and authority of Council; do not support authority to reverse	

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
Council, described above, which would also oversee the communication of lessons learned to review staff, as well as potential follow-up action.		decisions.	
SCIENCE REPORT			
The 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 (21 USC §360c(a)(3)(D)(ii) and 21 USC §360c(i)(1)(D)). CDRH should clearly and consistently communicate that, while the "least burdensome provisions" are, appropriately, meant to eliminate unjustified burdens on industry, such as limiting premarket information requests to those that are necessary to demonstrate reasonable assurance of safety and effectiveness or substantial equivalence, they are not intended to excuse industry from pertinent regulatory obligations nor to lower the Agency's expectations with respect to what is necessary to demonstrate that a device meets the relevant statutory standard.		✓ No need to revise guidance; train industry and FDA on existing guidance.	
The Task Force recommends that CDRH continue its ongoing efforts to improve the quality of the design and performance of clinical trials used to support premarket approval applications (PMAs), in part by developing guidance on the design of clinical trials that support PMAs and establishing an internal team of clinical trial experts who can provide support and advice to other CDRH staff, as well as to prospective investigational device exemption (IDE) applicants as they design their clinical trials. The Center should work to assure that this team is comprised of individuals with optimal expertise to address the various aspects of clinical trial design, such as expertise in biostatistics or particular medical specialty areas. The team would be a subset of the Center Science Council discussed in Section 4.2.1 of this report, and, as such, it may also serve in the capacity of a review board when there are differences of opinion about appropriate clinical trial design and help assure proper application of the least burdensome principle. CDRH should also continue to engage in the development of domestic and international consensus standards, which, when recognized by FDA, could help establish basic guidelines for clinical trial design, performance, and reporting. In addition, CDRH should consider expanding its ongoing efforts related to clinical trials that support PMAs, to include clinical trials that support 510(k)s.		✓ Include all stakeholders in development of guidance.	
The Task Force recommends that CDRH work to better characterize the root causes of existing challenges and trends in IDE decision making, including evaluating the quality of its pre-submission interactions with industry and taking steps to enhance these interactions as necessary. For example, the Center should assess whether there are particular types of IDEs that tend to be associated with specific challenges, and identify ways to mitigate those challenges. As part of this process, CDRH should consider developing guidance on pre-submission interactions between industry and Center staff to supplement available guidance on pre-IDE meetings.	✓		

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
The Task Force recommends that CDRH consider creating a standardized mechanism whereby review Offices could rapidly assemble an ad hoc team of experienced review staff from multiple divisions to temporarily assist with time-critical work in a particular product area, as needed, in order to accommodate unexpected surges in workload. This would need to be done in such a way that ad hoc teams would only assist with work that does not require specialized subject matter expertise beyond what the team members possess. The Task Force recognizes that such an approach is only a stop-gap solution to current workload challenges, and that additional staff will be necessary to better accommodate high workloads in the long term. The Center's staffing needs are discussed further below.		✓ Ensure routine work is not adversely affected; ensure oversight of team work.	
The Task Force recommends that CDRH assess and better characterize the major sources of challenge for Center staff in reviewing IDEs within the mandatory 30-day timeframe, and work to develop ways to mitigate identified challenges under the Center's existing authorities.		✓ Do not expend valuable resources; develop guidance for pre-IDE meetings.	
The Task Force recommends that CDRH continue ongoing efforts to develop better data sources, methods, and tools for collecting and analyzing meaningful postmarket information, consistent with the Center's FY 2010 Strategic Priorities. In addition, the Center should conduct a data gap analysis and a survey of existing U.S. and international data sources that may address these gaps. These efforts should be in sync with and leverage larger national efforts. As CDRH continues its efforts to develop better data sources, methods, and tools, it should invite industry and other external constituencies to collaborate in their development and to voluntarily provide data about marketed devices that would supplement the Center's current knowledge.		✓ Continued validation of data owners, research contractors, study methods, and data sets.	
The Task Force recommends that CDRH conduct an assessment of its staffing needs to accomplish its mission-critical functions. The Center should also work to determine what staff it will need to accommodate the anticipated scientific challenges of the future. CDRH should also take steps to enhance employee training and professional development to assure that current staff can perform their work at an optimal level. As part of this process, the Center should consider making greater use of professional development opportunities such as site visits or other means of engagement with outside experts in a variety of areas, including clinical care, as described below. This recommendation complements the Center's ongoing efforts under its FY 2010 Strategic Priorities to enhance the recruitment, retention, and development of high-quality employees.	✓		
The Task Force recommends that CDRH continue the integration and knowledge management efforts that are currently underway as part of the Center's FY 2010 Strategic Priorities. As part of these efforts, the Task Force recommends that CDRH develop more effective mechanisms for cataloguing the Center's internal expertise, assess the effectiveness of the inter-Office/Center consult process, and enhance the infrastructure and tools used to provide meaningful, up-to-date information about a given device or group of	✓		

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
devices to Center staff in a readily comprehensible format, to efficiently and effectively support their day-to-day work.			
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.		✓ Explain use of social media technology; ensure confidentiality of information; define expert selection process.	
The Task Force 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 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.	✓		
The Task Force recommends that CDRH 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. As it puts this approach into practice, CDRH should consider adopting several key principles. First, the process should allow for a range of individuals to participate in the deliberation phase, including managers and employees, to help take into consideration potentially cross-cutting issues and assure consistency in responding to new scientific information. To support this principle, CDRH should establish a Center Science Council, comprised of experienced employees and managers and under the direction of the Deputy Center Director for Science, to provide oversight and help assure consistency across the Center. Second, the process should be streamlined to allow for new information to be raised and addressed in a timely manner. Third, the process should include a mechanism for capturing in a structured manner the rationale for taking a particular course of action, so that it can be articulated clearly to staff and external constituencies and incorporated into the Center's institutional knowledge base. Fourth, the process should be designed to allow for prioritization of issues. The Center should also develop metrics to determine whether or not the new process is effective.		✓ Include industry in steps 3 and 4	
The Task Force recommends that CDRH enhance its data sources, methods, and capabilities to support evidence synthesis and quantitative decision making as a long-term goal.	✓		

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
The Task Force recommends that CDRH continue its ongoing efforts to streamline its processes for developing guidance documents and regulation, consistent with the Center's FY 2010 Strategic Priorities. For example, CDRH should explore greater use of the "Level 1 – Immediately in Effect" option for guidance documents intended to address a public health concern or lessen the burden on industry. CDRH should also encourage industry and other constituencies to submit proposed guidance documents, which could help Center staff develop Agency guidance more quickly.		✓ Ensure use of Level 1 is limited to public health concerns	
The Task Force recommends that CDRH establish as a standard practice sending open "Notice to Industry" letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations on the basis of new scientific information. CDRH should adopt a uniform template and terminology for such letters, including clear and consistent language to indicate that the Center has changed its regulatory expectations, the general nature of the change, and the rationale for the change. Currently, manufacturers typically learn of such changes through individual engagement with the Agency, often not until after they have prepared a premarket submission. The aim of issuing a "Notice to Industry" letter would be to provide greater clarity to manufacturers, in a timelier manner, about the Center's evolving expectations with respect to a particular group of devices. Because a change in regulatory expectations would represent a change in policy, a "Notice to Industry" letter would likely be considered guidance, although it would typically be issued relatively quickly and would generally not contain the level of detail traditionally found in other guidance documents. In the interest of rapidly communicating the Center's current regulatory expectations to industry, 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. To expedite the issuance of "Notice to Industry" letters, CDRH should develop standardized templates for these letters and, as necessary, their accompanying Federal Register notices. In addition, when appropriate, CDRH should follow "Notice to Industry" letters as soon as possible with new or modified guidance explaining the Center's new regulatory expectations in greater detail and revising the guidance where necessary in response to comments received, so that external constituencies have a fuller understanding of the Center's current thinking. CDRH should also consider creating a webpage for identifying and explaining new information that has altered the Center's regulatory expectations, so that, across all CDRH-regulated products, external constituencies can better understand the rationale for changes in the Center's requirements.		✓ Clearly define circumstances for use; establish implementation timeframes; make NIT public, not limited to current manufacturers	
The Task Force recommends that CDRH take steps to improve medical device labeling,			✓
and to develop an online labeling repository to allow the public to easily access this information. The possibility of posting up-to-date labeling for 510(k) devices online is			✓

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CDRH RECOMMENDATION	SUPPORT	SUPPORT WITH MODIFICATION	DO NOT SUPPORT
described in greater detail in the preliminary report of the 510(k) Working Group (described further in Section 3, below).			
The Task Force recommends that CDRH 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. The SOP should include the expectation that when a decision is made to take a particular course of action, including a change in evidentiary expectations, the action and its basis should be communicated clearly and promptly to all affected parties. If it is not possible to provide complete detail about the basis for an action due to confidentiality concerns, Center staff should share as full an explanation as is allowable and state why a more complete explanation is not permissible. In addition, Center leadership should take steps to make sure that all employees have an accurate understanding of what information they are permitted to discuss with manufacturers, so that information that would help clarify the basis for a particular action is not needlessly withheld.		✓ Involve all stakeholders in developing the procedure	
The Task Force recommends that CDRH continue its ongoing efforts to make more meaningful and up-to-date information about its regulated products available and accessible to the public through the CDRH Transparency Website, consistent with the Center's FY 2010 Strategic Priorities and the work of the FDA Transparency Task Force. In addition to the pre- and postmarket information that is already available on CDRH Transparency Website, the Center should move to release summaries of premarket review decisions it does not currently make public (e.g., ODE 510(k) review summaries) and make public the results of post-approval and Section 522 studies that the Center may legally disclose. Making such information readily available to the public will provide CDRH's external constituencies with greater insight into the data that guide the Center's decisions and evolving thinking.		✓ Do not post decisions of devices that were not cleared.	

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Specific Comments

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.*

"Same Intended Use"

Lack of a Clear Distinction between Terms

Recommendation: *The 510(k) Working Group recommends that CDRH revise existing guidance to consolidate the concepts of "indication for use" and "intended use" into a single term, "intended use," in order to reduce inconsistencies in their interpretation and application. Several public comments expressed concern that, if these two terms were combined, any proposed change in a device's label indications could be considered a change in "intended use." The Working Group recognizes the importance of providing submitters with the flexibility to propose certain changes to their labeling, without such a change necessarily constituting a new "intended use." Therefore it recommends that CDRH carefully consider what characteristics should be included under the term "intended use," so that modifications that are currently considered to be only changes in "indications for use" and that CDRH determines do not constitute a new "intended use," are not in the future necessarily construed as changes in "intended use" merely because of a change in semantics. Any change in terminology would be intended to provide greater clarity and simplicity, not necessarily to make the concept of "intended use" more restrictive. The Center should also carefully consider what it should call the existing "Indications for Use" statement in device labeling and the "Indications for Use" form currently required for all 510(k)s, in order to avoid confusion in terminology but still maintain an appropriate level of flexibility for submitters.*

AdvaMed does not support the consolidation of "intended use" and "indications for use" into a single term, and maintains that there is value in preserving these terms as separate concepts because the terms are not synonymous. It is critical that the two concepts remain distinct and separate, as they clearly serve different purposes. "Intended use" broadly describes the use of a generic type of device (i.e., what the device does) while "indications for use" more specifically describes the device's clinical uses and patient population(s). Combining the two terms may constrain the meaning of intended use, remove the flexibility that is currently afforded to the Agency in determining what new uses should be regulated within the confines of Section 510(k), and unnecessarily narrow the meaning of substantial equivalence. Indeed, combining the terms eliminates the distinction between "general" and "specific" uses that FDA has relied upon in determining whether the addition of a specific indication for use may trigger the need for additional data, including clinical data, versus the need for a PMA or a *de novo* classification.[2]

[2] *See* FDA Guidance for Industry: General/Specific Intended Use (1998). Available at: http://www.fda.gov/MedicalDeviceRegulationandGuidance/GuidanceDocuments/ucm073944.htm.

FDA has recognized that the addition of a specific indication may or may not alter a device's intended use, depending on a multitude of factors. Furthermore, removing the "Indications for Use" terminology from its tool box will result in confusion among patients and health care professionals who rely on the indications for use appearing in product labeling consistent with other FDA-regulated products. If, however, FDA determines that the intended use is altered, it will issue an NSE determination. FDA needs to retain the flexibility of considering those factors. From a patient perspective, we are concerned that patient access to new devices would be delayed because of a potential increase in Not Substantially Equivalent (NSE) determinations resulting from a combination of these two terms.

AdvaMed believes that the specific differences between the terms, "intended use" and "indications for use," can be clarified by developing definitions of each concept within the context of substantial equivalence. The Code of Federal Regulations (21 C.F.R. § 801.4) provides a definition of intended use in the context of postmarket behavior related to the need for adequate directions for use as described in 21 C.F.R. § 801.5, and indications for use is defined in the PMA regulations (21 C.F.R. § 814.20). Neither is defined for use in the context of substantial equivalence. With that in mind, AdvaMed recommends adding definitions in 21 C.F.R. Part 807 that clarify the use of these terms in the premarket notification context.

AdvaMed recommends amending 21 C.F.R. Part 807 to include a discussion of intended use and indications for use. We suggest that the following section be added to Part 807:

> **New Section § 807.80 *Meaning of Intended Use and Indications for Use***
> **The words *intended use* in § 807.100(b)(1) refer to a regulatory concept that determines the boundaries of use for a generic type of device. *Intended use* 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. The words *intended use* refer to the objective intent for the device function by the persons legally responsible for the proposed labeling of the device that is the subject of the premarket notification submission. *Intended use* describes what the device is intended to provide to the user and patient and for what purpose. Objective intent may be inferred from such persons' written or oral expressions, or the design of the device, however, for the purpose of determining substantial equivalence, the objective intent must be determined from the proposed labeling.[3] *"Indications for use"* provides a detailed, specific description of the specific target population(s) for the intended use that generally describes device function, and includes the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, and/or a description of the general or specific patient populations or anatomies for which the device is intended, as appropriate.**

[3] This aspect of our proposed definition of intended use derives from Section 513(i)(1)(E)(1) of the Act, which states that "[a]ny determination by the Secretary of the intended use of a device [for the purpose of determining substantial equivalence] shall be based upon the proposed labeling submitted in a report for the device under Section 510(k)."

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AdvaMed supports the development of guidance documents that *clarify* the meanings of "intended use" and "indications for use," rather than revising existing guidance to consolidate these terms, as recommended by the 510(k) Working Group. Examples distinguishing intended use from indications for use that could be provided in future guidance documents include:

- The *intended use* of an electrosurgical cutting and coagulation device is to remove tissue and control bleeding by use of high-frequency electrical current (21 C.F.R. § 878.4400). Electrosurgical cutting and coagulation devices, however, may be specifically designed to accommodate different anatomies. They may have *indications for use* in thoracic, gynecologic, ENT, or other procedures, as illustrated by the 31 product classification codes for electrosurgical instruments.

- The *intended use* of an infusion pump is to deliver fluid to a patient in a controlled manner (21 C.F.R. § 880.5725). External infusion pumps may have any of the following *indications for use*:
    - general administration of drug solutions vs. blood vs. insulin.
    - intravenous, epidural, subcutaneous, subarachnoid, etc.
    - patient-controlled analgesia
    - hospital versus home use

- The *intended use* of a gas analyzer is to provide a means of monitoring gas concentration and to alert clinical personnel when limits fall outside of a pre-specified range (there are over 15 classification regulations for gas analyzers). The indications for use of a gas analyzer could be for an anesthetic agent, or oxygen, carbon dioxide, or nitrous oxide.

AdvaMed notes that not all devices subject to 510(k) have both an intended use and an indication for use (e.g., a syringe delivers whatever liquid it contains, what it delivers is not specified, and there is no specific patient population). Also with respect to intended use, AdvaMed recommends that FDA take into consideration that intended use for *in vitro* diagnostic devices may include what is being measured, and for what purpose. However, the intended use should not extend to an IVD's particular performance characteristics (e.g., accuracy, ranges, or cut-off values).

AdvaMed also recommends that FDA continue the practice of attaching an "Indications for Use" form to all substantially equivalent (SE) letters. The Indications for Use form provides a transparent means through which all stakeholders are able to clearly identify the indications for use that have been accepted by FDA. Because of the significant impact of any modifications to the definitions of intended use and indications for use, we believe it is necessary for the Agency to provide notice and an opportunity for public comment.

AdvaMed supports the Working Group's recommendation that the Indications for Use statement (if any) be included in the *labeling* but that it should not be provided directly on the package *label*. Further, some packages are not sized to contain this information and there is an

environmental issue associated with increased packaging. This requirement would necessitate the amendment of 21 C.F.R. Part 801, requiring notice and comment. Users are provided with the product labeling, which already contains the Indications for Use.

Insufficient Guidance for 510(k) Staff and Industry

Recommendation: *The 510(k) Working Group recommends that CDRH develop or revise existing guidance to clearly identify the characteristics that should be included in the concept of "intended use."*

AdvaMed supports the revision of existing guidance to clarify the terms "intended use" and "indications for use," but does not support the recommendation to consolidate these terms.

Recommendation: *The 510(k) Working Group further recommends that CDRH provide training for reviewers and managers on how to determine "intended use." Such training should clarify the elements of a device application that should be considered when determining the "intended use," e.g., product labeling, device design (explicit or implied), literature, and existing preclinical or clinical data. Training on "intended use" should also be provided to industry.*

If FDA adopts AdvaMed's recommended definition of "intended use" and "indications for use," then FDA should conduct training of review staff on to determine these terms.

Off-Label Use

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

AdvaMed does not support this recommendation. AdvaMed does not agree with granting additional authority to FDA when the Agency believes that a device's primary intended use is an off-label use that is not reflected in the proposed labeling. FDA currently has statutory authority to act on off-label use that could cause harm by requiring a statement in the product labeling.

Congress has previously addressed this issue. In the Food and Drug Administration Modernization Act of 1997 (FDAMA), Congress clearly defined the approach the Agency must take when identifying concerns regarding potential off-label use of devices undergoing 510(k) review. This approach, codified at Section 513(i)(1)(E)(i) of the Act,[4] provides that the

[4] 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

Agency's determination of intended use "shall be based upon the proposed labeling," but that the Agency may address concerns about potential off-label use through requiring a statement in the labeling, after consulting with the applicant and if the following criteria are met: if 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 if such use could cause harm.

We do not believe that there is a need for any further restrictions on 510(k) clearance related to potential off-label use. A properly administered 510(k) program ensures that devices receiving FDA clearance are suitable for the intended use and indications for use in the proposed labeling for which they are being cleared. The determination of substantial equivalence should not take into account potential off-label uses, and clearance should not be withheld for the requested use pending submission of data for a suspected off-label use that the sponsor has not requested. Instead, the statute directs CDRH to address those concerns by requiring statements in the labeling, including limitations within the intended use statement -- without otherwise affecting a substantial equivalence determination. This Congressionally-mandated path provides a more flexible path for CDRH to follow while protecting public health, and is less onerous for both the Agency and industry.

AdvaMed does not support the expansion of FDA's authority to consider an off-label use as the primary intended use. This expanded authority would place reviewers in the untenable position of second guessing the sponsor's intentions and would be disruptive to the 510(k) program. Further, a 510(k) could automatically receive an NSE determination if the sponsor has not provided data on what FDA presumed to be the primary use, thereby leading to an NSE decision for the legitimate 510(k) use requested by the sponsor.

Companies with the intent to market a device for a legitimate intended use should not be prevented from obtaining 510(k) clearance because other product uses may exist. 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." Further, the possibility of a CDRH decision to require a company to support an additional intended use may result in the company's decision not to pursue commercial development of a new and potentially useful device or diagnostic, further stifling innovation. Additionally, such a requirement could represent an undue hardship to a smaller company that does not have the economic means to pursue a use it did not intend.

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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."

As noted above, where CDRH has concerns that there is a reasonable likelihood that the device will be used outside of the proposed labeling and when that use potentially could cause harm, it now issues an "SE with limitations" decision and requires manufacturers to include adequate warnings against such use in the labeling. Likewise, in the postmarket period, the Agency has the ability to deal with manufacturers that engage in off-label promotional activities. Specifically, 21 C.F.R. § 801.4 provides the Agency with considerable discretion in identifying off-label uses and company activities geared toward off-label promotion. When these situations arise, FDA can take many actions to stop off-label promotion and to encourage compliance with applicable requirements.
When substantial off-label use is discovered in the postmarket period and the company has not illegally promoted such use, FDA should encourage companies to seek clearance for the off-label use and to develop adequate directions for use for these new clinical applications, or to add or maintain a specific limitation in labeling for the device. In instances where the company wishes to include the off-label use(s), FDA should work with the company to identify the type of data required to support an expanded use.

Different Questions of Safety and Effectiveness

Inconsistent Terminology

Recommendation: *The 510(k) Working Group recommends that CDRH reconcile the language in its 510(k) flowchart (shown on page 27 of this report) with the language provided in section 513(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360c(i) regarding "different technological characteristics" and "different questions of safety and efficacy."*

AdvaMed does not support the 510(k) Working Group's recommendation that the language in FDA's 510(k) flowchart and the statutory language in 513(i) of the Act be reconciled. As reflected in Blue Book memorandum K86-3, the Agency has interpreted "different questions" to be "new types of questions." AdvaMed believes that the current wording in the flowchart fits within the intent of the statute. It is a long-standing and well-established interpretation that has worked well for many years. By inserting the words "new types," it is our understanding that the Agency was indicating that different questions can be grouped in a manner that provides FDA appropriate discretion in deciding what scientific questions justify making a new device NSE on this basis. As a result, any modification of this well-established approach is a new interpretation, which requires notice and comment.

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Insufficient Guidance for 510(k) Staff and Industry

Recommendation: *The 510(k) Working Group recommends that CDRH revise existing guidance to provide clear criteria for identifying "different questions of safety and effectiveness" and to identify a core list of technological changes that generally raise such questions (e.g., a change in energy source, a different fundamental scientific technology).*

AdvaMed supports the Working Group's recommendation for clear guidance, subject to notice and comment, focused on the use of risk assessments in identifying potential "new types of safety and effectiveness questions." The use of flowcharts differentiating elements for consideration would further clarify the process.

Recommendation: *The 510(k) Working Group further recommends that CDRH develop and provide training for reviewers and managers on how to determine whether a 510(k) raises "different questions of safety and effectiveness." Training on "different technological characteristics" and "different questions of safety and effectiveness" should also be provided to industry.*

AdvaMed supports the Working Group's recommendation to train reviewers and managers on "new types of safety and effectiveness questions." Training should be provided to reviewers, managers, and industry so that all understand that when questions are raised by a new technology, and they can be answered by established and/or recognized standards, or established, recognized, or validated test methods, then an NSE determination is not the automatic result. AdvaMed further recommends that CDRH focus on clarifying which questions of safety and efficacy are "different," or "new types," rather than on the underlying device technology and its characteristics.

AdvaMed believes that a question of safety and effectiveness is not "different" if the question can be answered through established, well recognized, or validated test methods. Advances in materials science provide examples of how specific scientific questions can be approached in the context of SE decision-making. In the medical device industry, manufacturers constantly search for new materials. As new materials are identified, questions often arise regarding their suitability for a particular use. While the use of a new material in a device may raise questions, historically FDA has considered the question to be of the same "type" that previous materials have raised and, therefore, have not generally viewed changes in materials as a justification for a NSE decision. As an alternative to considering which questions are of the same type and which are not, focusing on what testing is required to address the question, and whether the testing involves well established and recognized methods removes much of the subjectivity. In the context of the latest materials science, questions regarding a new material's ability to meet the demands of a particular use environment can usually be addressed through bench and animal testing.

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.*

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Concerns about Predicate Quality

Recommendation: *The 510(k) Working Group recommends that CDRH consider developing guidance on when a device should no longer be available for use as a predicate because of safety and/or effectiveness concerns. It is expected that such a finding would be an uncommon occurrence. Any factors set forth in guidance regarding when a device should no longer be used as a predicate should be well-reasoned, well-supported, and established with input from a range of stakeholders, and unintended consequences should be carefully considered.*

AdvaMed does not support the Working Group's recommendation that CDRH develop guidance on when a device should no longer be available for use as a predicate. AdvaMed believes that statutory change is required to disqualify a legally marketed device from being available for use as a predicate because of purported safety or effectiveness concerns, and cannot be accomplished by guidance. AdvaMed does not believe, however, that it is necessary to promulgate new legislation, as FDA already has the authority to remove violative devices from the market. Under Section 513(i)(2) of the Act, those devices that have been removed from the market by FDA or have been determined adulterated or misbranded by a judicial order are disqualified from being predicate devices. Simply put, guidance documents cannot create requirements and cannot supersede statutory law. CDRH's current statutory remedy to a device that it believes is unsafe or ineffective is to bring an enforcement action to remove the device from the market (i.e., the Agency may ban the device). In addition, if the controls for assuring safety or effectiveness are inadequate, CDRH can develop special controls or reclassify the device. Using guidance to shortcut the statute is without legal basis and unacceptable.

The 510(k) Working Group's concerns appear not to be relevant to 510(k)s reviewed by the Office of *In Vitro* Diagnostics (OIVD). OIVD informs companies of the product or technology to which the 510(k) device must be compared (gold standard: e.g., bacteriological media/culture for many infectious diseases), thereby reducing the risk of safety and effectiveness concerns with the predicate device(s).

AdvaMed further notes that there are a number of older devices that remain relevant to current standards of care or remain popular because they represent a more affordable option than the latest technology. There also may be attributes of older predicate devices that are relevant to the newer technologies. AdvaMed also notes that devices evolve as new technological advances are made, and are not expected to be identical to the older predicate devices. For example, if FDA has concerns about the safety and effectiveness of a legally marketed device, those concerns may not apply to the 510(k) device because of technological improvements, and FDA has full statutory authority to require evidence that the technological characteristics of the new device do not raise new/different safety and effectiveness concerns. Finally, AdvaMed notes that not all devices are removed from the market because of reasons that would disallow their use as a predicate (i.e., safety and effectiveness concerns). For example, companies will discontinue a product line for business reasons unrelated to safety and effectiveness.

Rescission Authority

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

AdvaMed does not support the issuance of a regulation to exercise rescission authority nor does AdvaMed support expansion of rescission authority. AdvaMed believes that, absent the commission of an act of fraud in establishing the substantial equivalence of a device, rescission would not be justified and should not be allowed, because of the "domino effect" it could have. If FDA had the authority to 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 jeopardized (i.e., the device would be misbranded), even if the concerns that prompted the rescission of the predicate device do not apply to the subsequent devices. Expanding FDA's 510(k) rescission authority to include rescission based on safety or effectiveness concerns is not only unnecessary, it also would cause more harm than good for several reasons. The 510(k) clearance system is a classification process and is based on predicates. Once a device is cleared and FDA has made the decision that its design and intended use are substantially equivalent to a predicate device, FDA should not rescind that decision because, for example, a device is manufactured under poor conditions that impair its safety or effectiveness or because a manufacturer has changed the device's design. If a predicate, key to a line of subsequent devices, is rescinded, it could result in each and every device that cites the rescinded device being rescinded as well, even when those devices do not share whatever defect occurred in the rescinded device, with a potentially significant impact to public health. As noted above, FDA currently has the tools to isolate a device that violates any part of the Act, is determined not to be substantially equivalent to a predicate, or is not safe and effective to protect the public health without creating unreasonable jeopardy for innocent parties.

The Act provides FDA with numerous tools to remove violative devices from the market and should not accomplish it in a way that may broadly limit access to safe and effective medical devices, thus undermining the public health. If a device is considered unsafe because it is manufactured under noncompliant GMPs, is manufactured incorrectly, or the manufacturer has changed the design without meeting the appropriate 510(k) premarket requirements, then that device should be appropriately dispositioned per FDA's current postmarket authorities provided in the Act. These authorities include reclassification, recall, warning letters, and other enforcement actions. In addition, the Act already provides for the banning of a medical device in situations of substantial deception or unreasonable and substantial risk of illness or injury.[5] Banned medical devices can no longer be legally marketed and can therefore not be cited as a predicate device. FDA also has the authority to issue an order for mandatory device recall[6] or to

[5] See Section 516 of the Act

[6] See Section 518 of the Act

reclassify a device.[7] FDA also may, when necessary, obtain court orders for product seizure. These conditions can be remedied, however, and should not be used as grounds for revoking the original 510(k) decision, because the currently available statutory tools enable the Agency to protect the public health and also maintain the integrity of the classification system.

AdvaMed agrees that FDA can nullify a substantial equivalence determination, if the 510(k) submitter procured the determination through fraud, or if the Agency made an inadvertent administrative mistake or error and corrected it prior to the order becoming final. Rescinding one 510(k) clearance could potentially reclassify a group of devices, and FDA does not need to take such action in order to protect the public health. The Act provides the Agency with numerous efficient means to remove unsafe or violative devices from the market. Moreover, the Act authorizes FDA to reclassify devices based on new information, including reassessment of past information in the administrative record.

In summary, FDA does not have express or implied statutory authority to rescind 510(k) classification determinations, nor are there compelling policy grounds to do so. The Working Group indicated that rescission would be seldom used in response to particular circumstances; we believe the law now provides adequate remedies for any such circumstance and fully provides adequate protection of the public health if the Agency is willing to use the remedies Congress gave it to ensure safe and effective devices. Outside of the limiting circumstances described above, undermining the predicate status of a device through rescission would not advance the public health and would undermine the entire classification system set forth in the Act.

Please see the detailed legal analysis of FDA's proposed expanded rescission authority provided in Attachment B.

Use of "Split Predicates" and "Multiple Predicates"

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

AdvaMed is opposed to disallowing the use of split predicates and supports the use of multiple predicates. The current bundling guidance works well for bundled submissions, and the only revision necessary is to clarify the distinction between multi-parameter or multiplex devices. AdvaMed supports updating CDRH's existing bundling guidance only to clarify the distinction between multi-parameter or multiplex devices. AdvaMed believes that the use of multiple predicates, i.e., using more than one predicate where each predicate individually supports substantial equivalence, is and should continue to be permissible under the 510(k) process.

[7] See Section 513(e) of the Act.

A 510(k) submission utilizing multiple predicates must still provide a clear demonstration of safety and effectiveness. Further, disallowing the use of "split predicates" and/or arbitrarily disallowing the use of 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, resulting in delayed or no patient access to new devices. The bases for our positions are detailed below.

"Split" Predicates

In its August report, FDA defined "split" predicates as taking the intended use from one device and the technology from another device and putting those two together to try to reach a substantial equivalence determination. Per statute, the new device must always have the same intended use as the predicate device. Different technology is permissible provided that the different technology does not raise new or different types of questions. First and foremost, and as noted above, AdvaMed opposes disallowing the use of "split predicates." Such an action will stifle innovation and evolutionary change in device design, which the 510(k) program was designed to encourage.

The use of split predicates is a reasonable approach to showing substantial equivalence. We believe the use of a split predicate is vital to innovation and to the public health goals of the 510(k) program because many devices are modular in nature (i.e., they are made up of a combination of components). AdvaMed believes that FDA should allow the submission of 510(k)s in accordance with actual product configuration, enabling the use of split predicates where appropriate.

In cases where split predicates are used, the 510(k) sponsor should be required to provide risk-based justification for using split predicates for their particular device. This risk-based approach is consistent with the concepts behind "multiple predicates" and the dual goal of CDRH to protect public health while encouraging device innovation. Guidance documents should include CDRH's current thinking on acceptable risk-based justifications to encourage high-quality 510(k) filings. Further, reviewers should be trained on the use of split predicates.

Split predicates add to the dataset for FDA to consider in a useful manner. While there is often a "core" predicate based on intended use or mode of action, it may not seem comparable owing to a different feature such as power source, materials, or technology. Being able to demonstrate to FDA that there is marketing experience to be drawn upon for this different feature allows FDA to consider all of the available information and make an informed judgment as to the level of risk introduced by the new product.

Please note that the IVD practice of providing performance data against both a "gold standard" and a predicate is not the same as the use of split (or multiple) predicates. The data from the reference method, or gold standard, are meant to provide additional information on the IVD's accuracy as compared to a recognized method, not to demonstrate substantial equivalence. The predicate is used to demonstrate substantial equivalence.

Multiple Predicates

Since 1986, the Agency has recognized the concept of multiple predicates in cases where new devices and multiple predicates have compatible intended uses. Specifically, in a 1986 guidance,[8] FDA stated that a new device made up of a combination of devices of different types and classifications could be substantially equivalent to multiple predicates; however, the classification of the new device would be that of the highest classification of the predicates relied upon to show substantial equivalence. By extension, multiple predicates for new devices within the same generic type are permissible and consistent with FDA's longstanding interpretation of its premarket notification classification provisions.

AdvaMed supports the development of guidance for use of multiple predicates, but does not support any guidance that arbitrarily restricts the number of predicate devices that can be used. FDA should expect a 510(k) submission to provide a clear demonstration of safety and effectiveness, and that the aggregate of the components does not create new or different questions of safety or effectiveness. To curtail such an approach would, in some cases, require multiple, step-wise 510(k)s that would significantly delay introduction of more practical technology and would burden the review system with unnecessary 510(k)s.

Even if FDA were to eliminate the ability for 510(k) submitters to rely on multiple predicates, new devices that incorporate features of more than one legally marketed Class I or Class II device could still be classified into either class under the *de novo* process and could then serve as predicates for subsequent devices. The *de novo* classified device could then serve as a predicate for each of the predicates that would have been cited if a multiple predicate approach had been allowed. In other words, changing the Agency's historical use of multiple predicates elevates form over substance and fails to advance the public health while creating extra work and protracted timelines for FDA and industry.

More than Five Predicates

As noted above, AdvaMed also opposes the Working Group's proposal to prohibit more than five predicate devices. As noted by the Working Group, multiplex devices could represent more than five predicate devices' functionality. Indeed, some innovative technologies, like microarrays, could require well over the five-predicate limit. Furthermore, as devices become more complex and attempt to combine more features for both convenience and economy, the need to reference multiple predicates will increase. 510(k) sponsors should be provided the opportunity to propose and justify within the submission the use of multiple predicate devices. The effect of limiting the number of predicates could result in multiple 510(k)s where one submission would have sufficed, putting further pressure on scarce FDA resources.

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[8] *Guidance on the Center for Devices and Radiological Health's Premarket Notification Program* (*Blue Book Memo. #K86-3*) (June 30, 1986) at 13.

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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.*

AdvaMed supports reviewer training on submissions with multiple predicates, and on the current bundling guidance. We further recommend that similar training be offered to the manufacturing community to ensure high-quality, consistent 510(k) submissions for CDRH to review. AdvaMed offers to partner with CDRH to conduct workshops to disseminate such training to the medical device manufacturing community.

Also, please note that, bundling is a useful and efficient submission and review method, particularly in the IVD arena. For example, if a manufacturer of diagnostic instruments makes a change to a family of instruments, CDRH can review the change only once, instead of multiple times. Likewise, a reagent for use on multiple instruments within a family could be adequately reviewed once. For IVDs, for which a Pre-IDE meeting that discusses the content of the bundled submission has been held, a well-written single 510(k) can be efficiently reviewed and cleared within the current 90-day performance goal.

Recommendation: *The 510(k) Working Group further recommends that CDRH conduct additional analyses to determine the basis for the apparent association between citing more than five predicates and a greater mean rate of adverse event reports, as shown in Section 5.1.2.3 of this report.*

AdvaMed does not support the analyses proposed by the Working Group because we believe that there is no basis to correlate adverse event data to the number of predicates in a submission, as the Working Group did in their report. FDA is implying that it has the ability, through the 510(k) process, to reduce the mean rate of adverse event reports by reviewing several step-wise 510(k)s for a product with multiple predicates, rather than one 510(k) for a product with multiple predicates. AdvaMed does not understand this reasoning, as submission and clearance of 510(k)s are based on data and evidence, which should be the same whether multiple 510(k)s or a single 510(k) is submitted.

Regarding the greater mean rate of adverse event reports for devices with multiple predicates, we recommend that a formal investigation and determination of root cause of the adverse event be undertaken before inferring that the 510(k) process is responsible.

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 from eligible devices.*

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

AdvaMed strongly supports (1) revision of existing guidance on the *de novo* classification process; (2) pre-submission meetings to discuss data requirements for a *de novo* classification; and (3) a generic set of special controls that can be augmented with device-specific special controls as needed. Strengthening and optimizing the *de novo* process through a well-defined regulatory pathway will benefit the Agency, industry, and patients. This under-utilized 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. Indeed, if CDRH were to adopt a risk-based approach, some products that are currently subject to PMA could potentially be more efficiently and effectively reviewed through the *de novo* process.

AdvaMed recommends that FDA eliminate the need to submit a 510(k) and receive an NSE determination before requesting *de novo* down-classification, so that it becomes a "one-step" process, rather than a two-step process. As part of the one-step process, FDA should implement use of a pre-review process for a *de novo* submission (i.e., a "Pre-IDE"), where FDA and the sponsor agree to use of the *de novo* process as a viable pathway as well as to the content requirements of the *de novo* submission. Early utilization of a scientific panel of experts, when needed, could benefit this pre-review. We suggest that the sponsor requesting the *de novo* classification provide completed hazard analyses in the "Pre-IDE" document and a decision-making matrix, or algorithm, using FDA-recommended templates, which could be based on current ISO 14971. The content of the *de novo* should include supportive evidence to allow the Agency to fully evaluate the risks and benefits of the device. Clinical trials or clinical data should not be an automatic requirement of a *de novo* submission; however, the hazard assessment and decision-making matrix should clearly document whether these studies are required.

AdvaMed recommends that the existing guidance for assessing the eligibility of devices for *de novo* review be revised to include the following information:

1. A determination of whether the device has a different intended use or the same intended use but has new technology as compared to the named predicate device(s) that raises different questions of safety and effectiveness.

2. A hazard analysis and Special Controls document template, including reference to ISO 14971 - *Medical devices -- Application of risk management to medical* devices *for assessing the types of risks associated with new technologies or those associated with a new intended use.*
3. A flowchart with key decision criteria (similar to the flowchart used in "Deciding When to Submit a 510(k) for a Device Undergoing a Change" guidance). We note that OIVD already employs the use of a similar flow chart.
4. We suggest that the flowcharts include the following (this list is not inclusive):
    a) Is the device a prescription device, over-the-counter (OTC), or point-of-care (POC) device?
    b) Are there existing clinical data on the use of this device (e.g., outside of the U.S.)?
    c) Identify any hazards that the device poses to individual or public health.
    d) Identify the probability of harm.
    e) Does the device directly diagnose a particular disease or condition or is the device used in conjunction with other tests to establish an overall understanding of the clinical condition of patient?
    f) What is the likelihood that the device could malfunction or the malfunction could be undetected?
    g) What is the severity of harm if the device malfunctioned or was misused? Are there general or specific controls available to reduce the likelihood or severity of the malfunction? What are they?
    h) Will a new special control guidance document reduce the likelihood or severity of harm?
    i) If, with special controls, the likelihood of the malfunction to occur is high, and the severity of harm is high (death or serious injury), then not eligible for *de novo* classification.
    j) If special controls will significantly reduce the likelihood of malfunction and greatly limit severity of injury, then review as *de novo*.

As identified in FDA's 510(k) report, a generic set of special controls for devices reviewed under the *de novo* process could be a good step to strengthening and streamlining the process and providing clear parameters at the outset. A generic set of special controls more like the essential principles of the Global Harmonization Task Force (GHTF) would provide a means to create a consistent evidentiary standard for *de novo* reviews, and would minimize movements toward the full PMA set of requirements – as is appropriate because the *de novo* process was intended to be an alternative process for FDA to classify the device into Class I or Class II. To increase consistency in the process, we recommend the creation of a template identifying these generic special controls, as well as consideration of a standard submission format similar to the Global Harmonization Task Force Standard Technical Document (GHTF STED) format. Moreover, to the extent these generic special controls replace the product-specific special controls currently required under the *de novo* process, we encourage CDRH to publish detailed decision summaries

that provide industry with sufficient detail to understand CDRH's specific thinking related to specific devices. Further, to increase the efficiency of the *de novo* process, we recommend clear guidance on how to effectively use a Pre-IDE meeting in the context of the *de novo* process. As noted previously, elimination of the current process of having to file a 510(k) and receive an NSE determination as a pre-requisite to filing a *de novo* request would streamline the process considerably.

Again as noted in FDA's report, we agree there is merit in minimizing the time spent on the 510(k) review for a product that clearly is *de novo*. The review should focus on what in addition may be needed for the next level review. The evidentiary expectations for classification should be clearly communicated to the applicant, including the use of pre-submission meetings, where appropriate. The use of a generic set of special controls more like the GHTF principles would assist in focusing and clarifying this process.
Lastly, because of the importance of developing this pillar of FDA's regulatory framework, we recommend the Agency consider holding a public meeting on this process and working with the industry and other stakeholders to optimize this process.

2. Well-Informed Decision Making

RECOMMENDATION: *CDRH should take steps through guidance and regulation to facilitate the efficient submissions of high-quality 510(k) device information, in part by better clarifying and more effectively communicating its evidentiary expectations through the creation, via guidance, of a new "class IIb" device subset.*

Unreported Device Modifications

Recommendation: *The 510(k) Working Group recommends that CDRH revise existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k), and, for those modifications that do warrant a new 510(k), what modifications are eligible for a Special 510(k).*

AdvaMed supports the recommendation to update the existing guidance (K97-1) to clarify what types of modifications do or do not warrant submission of a new 510(k). While we agree this guidance is due for a review/update, this is a good guidance that has proved useful to FDA and industry over the years. At CDRH's request, AdvaMed submitted suggestions for improvements to the guidance in May 2010. We noted that the use of flow charts to assess changes has been especially helpful and provided input on what areas needed clarification. Consideration of the risk evaluation process as a means to assess changes rising to the level of a new filing is recommended.

The 510(k) Working Group, in its description of the history of Section 510(k), describes the implementation of the New 510(k) Paradigm. In addition to the information provided in the Preliminary Report, it is important to recognize that the 510(k) Paradigm was introduced at a period in time when the CDRH review process had slowed down to such a degree that serious concerns were raised that public health was not being promoted and innovation was being stifled. In response, CDRH developed a number of means, of which the Special 510(k) was one, to obtain essential information on device modifications, while imposing the least possible burden on industry and the Agency to enable protection of the public health. It also is noteworthy that FDA received the Hammer Award for Re-invention of Government from the Clinton Administration, in recognition of the importance and value of this initiative. AdvaMed believes the current process has merit; that it adequately protects the public health while encouraging innovation.

In support of its recommendation to identify the modifications that are eligible for a Special 510(k), the FDA Working Group cites Medical Device Report (MDR) data from CDRH's databases that suggest the MDR rate for devices that were cleared through the Special 510(k) process is slightly higher than for Traditional or Abbreviated 510(k)s. As noted, CDRH believes that the total number of MDRs likely is under-reported and that MDRs frequently do not cite the 510(k) number of the device associated with the adverse event. The conclusion reached is that further analysis would need to be conducted. AdvaMed believes it is premature to reach any conclusion about the effectiveness of the Special 510(k) or limiting the devices whose modifications are eligible for Special 510(k).

AdvaMed does not agree that the MDR data accurately reflect the Special 510(k) process. FDA has recognized that the reporting system, as good as it is, is limited. Likewise, information presented by Professor Ralph Hall to the Institute of Medicine (IOM) for its review of the 510(k) process indicates that MDR data are not good tools to judge performance of the 510(k), for the following reasons: highly variable reporting rates, reporting of inaccurate information, reporting of unconnected events, lack of quality control, and lack of confirmation. Hall suggests that recall information may be a better indication.

Professor Hall, in his assessment of the 510(k) process, looked at the relationship between Class I recalls and 510(k)s. He found that only 0.22% of Class I recalls were associated with 510(k) and related to premarket issues. Professor Hall did not find a relationship between Special 510(k) and Class I recalls. Interestingly, he found a similar rate of Class I recalls for devices subject to Premarket Approval. Dr. William Maisel, formerly of the Medical Device Safety Institute at the Beth Israel Deaconess Medical Center, who also looked at recalls, found a slightly higher rate of recalls associated with devices subject to Special 510(k)s. Combined with Professor Hall's data, this would indicate that the higher rate of recalls for devices subject to a Special 510(k) were not Class I recalls, but Class II or III recalls, representing moderate or minimal risk to public health. A report commissioned by AdvaMed and conducted by the Battelle Institute (Attachment A), confirms that the risk of recall related to use of the Special 510(k) process is not significantly higher than 510(k) products cleared through relative to CDRH's other review pathways.

As noted above, there are definite benefits associated with the use of the Special 510(k), most importantly the appropriate allocation of FDA resources for review of minor modifications to manufacturers' own devices. Design control requirements ensure that companies perform and document a thorough analysis of risks and potential risks associated with a specific device and have risk management programs to mitigate all risks. Companies also have a great deal of information, including information available to FDA, regarding the prior generations of the device. This information is used as inputs into the design control process. All of the information within the Design History File is available to FDA during routine inspections of manufacturers and FDA can, if needed and it is germane to the issue of substantial equivalence, request this information as part of any premarket review process. However, either limiting the scope of the Special 510(k) process or routinely requesting this information could impose an unnecessary burden on CDRH and the industry, without any corresponding benefit.

Recommendation: *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.*

AdvaMed does not support this recommendation for all Class II devices. This recommendation by the Working Group does not address the fundamental root causes identified in the discussion of unreported device modifications leading to the Working Group's recommendation. The examples cited, such as misuse of the Special 510(k) process, are more appropriately addressed within the Agency's current guidance, specifically the conversion of Special 510(k)s to Traditional 510(k)s, and compliance enforcement actions for extreme cases, as described in the Case Study: Unreported Modifications (pp 68-69).

The recommendation may be appropriate, provided that the definition of "any modifications" is narrowed and made relevant to changes with unclear impact on safety or effectiveness, in the context of a small, focused subset of Class II devices. It is not warranted for all Class II devices, or for the "Class IIb" subset proposed by FDA.

The periodic update is not necessary for all Class II devices, (see attached AdvaMed proposal on a small, focused subset of Class II devices, Attachment C), and would impose an unnecessary burden on FDA resources and on industry. It is the responsibility of the 510(k) holder to determine what modifications require a new 510(k) based on regulation and guidance, and FDA currently has a means to evaluate the appropriate reporting of device modifications through the facility inspection program. Changes to a device are routinely reviewed in the course of an FDA inspection of a company's design control procedure and other Quality System Regulation requirements. Revised guidance (K97-1), reflecting FDA's current thinking on device modifications that require a new 510(k), would also aide appropriate decision-making.

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Quality of Submissions

Lack of Clarity

Recommendation: *The 510(k) Working Group recommends that CDRH consider adopting the use of an "assurance case" framework for 510(k) submissions. An "assurance case" is a formal method for demonstrating the validity of a claim by providing a convincing argument together with supporting evidence. It is a way to structure arguments to help ensure that top-level claims are credible and supported. If CDRH pursues this approach, the Center should develop guidance on how submitters should develop and use an assurance case to make adequate, structured, and well-supported predicate comparisons in their 510(k)s. The guidance should include the expectation that all device description and intended use information should be submitted and described in detail in a single section of a 510(k). The guidance should also clearly reiterate the long-standing expectation that 510(k)s should describe any modifications made to a device since its previous clearance. CDRH should also develop training for reviewers and managers on how to evaluate assurance cases.*

AdvaMed does not support this recommendation. Adopting the general use of assurance cases is premature and unwarranted. As the Working Group points out in its recommendations, the "assurance case" framework is not widely used in the medical device industry, either by industry or by FDA. This raises two immediate concerns to industry. First, given that the Working Group clearly indicates that lack of adequate reviewer and industry training is a general concern relevant to the current perceived inconsistency of 510(k) reviews, this would impose yet another new training requirement on a Center that is already struggling to ensure adequate training of existing and new staff. The second concern is that it is not clear what problem is leading FDA to make this recommendation and whether the assurance case is the only or best means of addressing the concern raised by FDA.

The example FDA cited in support of using assurance cases is one where a labeling change in an earlier generation of device was not sufficiently highlighted by the submitter and the reviewer overlooked the change in making a substantial equivalence determination. The Working Group states that all intended use information should be submitted and described in detail in a single section of the 510(k). That simple recommendation would be easy to implement and would require very little in the way of additional training for reviewers or industry. The FDA Working Group also repeats the long-standing expectation that 510(k)s should describe any modifications made to a device since its previous clearance. Even without the use of an assurance case, these two simple changes would provide that any modifications to a device would appear in two sections of any future 510(k), thus limiting the likelihood that assurance cases would be overlooked by FDA reviewers. The FDA has not made the case that they will improve 510(k) submissions for simpler devices. Nor have they made a case for why change is necessary.

Recommendation: *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.

AdvaMed does not support requiring the submission of detailed device photographs or schematics nor does it support the release of detailed photographs and other graphic depictions to the enhanced 510(k) database. It is important to acknowledge that the release of any confidential or proprietary information to the public must be done with the permission of the owner of the information, in this case, the sponsor of the 510(k) submission. Schematics generally provide engineering information (e.g., wiring diagram) that is usually considered proprietary. The same could be said of "detailed" photographs depending on the level of detail required. Any photographs or graphic depictions of a device that would provide proprietary information to competitors, both domestic and outside the United States, therefore, should not be released to a publicly available website.

AdvaMed recognizes that having a visual image of the device under review may benefit the review process and we support the submission of photographs and drawings of the device (showing the external features) that are necessary to establishing substantial equivalence. As stated in the CDRH Preliminary Internal Evaluation, many companies currently provide depictions of the device under review. However, it is important to note that at the time of 510(k) submission, the final version of the device may not be available. In addition, there are some device types, such as software, for which a schematic or photograph is not relevant. Where appropriate, CDRH may ***request*** a photograph or graphic depiction of the device under review as a means to aid the review process and serve as an educational tool, but not state it as a requirement.

AdvaMed does not support *requiring* each 510(k) submitter to keep at least one unit of the device under review available for CDRH to access upon request. Under limited circumstances AdvaMed supports *requesting* submitters to keep one unit of the device available as a sample for CDRH to see during the 510(k) review process with the understanding that the device is used for education of the reviewer, is not appropriate for testing, and that the request does not delay the review of the submission. AdvaMed recommends that the request be made only when seeing the actual device is necessary for determining substantial equivalence, with FDA developing criteria and sharing them with the industry for when such a request for a device is appropriate. When a request is made, CDRH must consider the logistics related to such a request. Delivering large

pieces of equipment to FDA facilities makes little sense. Large pieces of equipment will require loading dock/receiving areas as well as secure storage within an appropriate storage environment. At any one time, CDRH could have thousands of devices requiring storage at the White Oak facility. If CDRH expects equipment to be operational, it may require special installation and calibration activities. It is also important to be mindful that in some cases it would be necessary for the reviewer to examine the device at the manufacturing facility because of device size or installation requirements. Devices such as X-ray equipment, robotic surgical equipment, and sterilization equipment would be expensive to ship, require installation by specialized technicians, and would occupy a large amount of space at CDRH.

In addition, keeping a device available indefinitely so it can be examined when it is cited as a predicate is impractical for industry and would provide limited benefit. Providing the space necessary to ensure secure storage with appropriate environmental conditions would present a financial and logistical burden on industry, especially on small companies with limited facilities, with no commensurate benefit to public health. Indefinite retention of devices, especially IVD products, with limited shelf-lives would not provide an accurate representation of the device after the use-before date has passed. In some cases, minor changes are made to devices during their marketed life. Retaining a sample of each version of the device would add to the storage burden.

CDRH also must recognize that a device sample submitted during 510(k) review might not be a product of the standard manufacturing process, but may be a manufacturing equivalent prototype or functional model. As noted, in some cases, the device in its final form may not exist at the time of 510(k) submission. In some cases, manufacturers may not be "in production" of a device that is not cleared by CDRH. Due to the many logistical issues as well as the possibility that a device may not be in its final configuration or not available at all, AdvaMed recommends that the availability of a sample device during the review be a CDRH *request* and not a requirement.

Improper Recognition of Standards

Recommendation: *The 510(k) Working Group recommends that CDRH provide additional guidance and training for submitters and review staff regarding the appropriate use of consensus standards, including proper documentation with a 510(k). CDRH should also consider revising the requirements for "declaration of conformity" with a standard, for example by requiring submitters to provide a summary of testing to demonstrate conformity, if they choose to make use of a "declaration of conformity."*

AdvaMed strongly supports the recommendations that CDRH provide additional guidance and training for industry and review staff regarding the appropriate use of consensus standards, including proper documentation within the 510(k).

Numerous domestic and international consensus standards address aspects of safety and/or effectiveness relevant to medical devices, and many of these standards have been developed with the participation of CDRH staff. A person required to submit a 510(k) must provide information as required by the statute and regulations to allow CDRH to make an appropriate decision

regarding clearance of the device. Conformance with recognized consensus standards plays an important part in satisfying some or all of these premarket review requirements.

Current guidance[9] states "CDRH believes that conformance with recognized consensus standards can support a reasonable assurance of safety and/or effectiveness for many applicable aspects of medical devices." For 510(k)s, information on conformance with recognized consensus standards helps to establish the substantial equivalence of a new device to a legally marketed predicate device. This information may be used to show that the new device is as safe and effective as the predicate in the areas covered by the standards. Moreover, if any premarket submission includes a declaration of conformity to recognized consensus standards that contain pass/fail criteria, this declaration should, in most cases, minimize the need for CDRH to review the actual test data for those aspects of the device addressed by the standards.

Existing FDA guidance on "Recognition and Use of Consensus Standards"[10] also addresses many of the issues noted in the 510(k) Report, and additional education on these topics would be particularly helpful to industry and FDA review staff:

- Conformance to a standard may not address all safety and efficacy questions about a device
- Only certain aspects of the standard may be recognized by FDA
- What documentation is needed regarding the appropriate use of standards, and any deviations from the standard
- Appropriate use of "declarations of conformity," with inclusion of the testing results, if the standard does not include pass/fail criteria

AdvaMed does not support revising the requirements for "declaration of conformity by requiring submitters to provide a summary of testing to demonstrate conformity. The guidance clearly notes that falsifying a declaration of conformity is a prohibited act under Section 301(x) of the Act. Therefore, requiring all submitters to provide a summary of testing to demonstrate conformity, even when the standard contains pass/fail criteria, is unnecessary, and would undermine the basic tenet of the Abbreviated 510(k) process, which is another important and valuable part of the 510(k) program.[11]

With the increased move toward globalization, AdvaMed urges FDA to continue to be involved in the standards development process and to formally recognize consensus standards early and to the fullest extent possible. We also strongly support the recommendations that CDRH provide additional guidance and training for industry and review staff regarding the appropriate use of those consensus standards, including proper documentation within the 510(k). We encourage

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9 Guidance for Industry and FDA Staff Recognition and Use of Consensus Standards. September 17, 2007.

10 Ibid.

11 See Section 514

CDRH to provide more concise examples of how manufacturers may be inappropriately using the standards, and how they might use them more effectively.

Incomplete Information

Recommendation: *The 510(k) Working Group recommends that CDRH should 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.*

AdvaMed does not support this recommendation for all submitters to provide this information. In its preliminary internal evaluation report, the FDA Working Group did, in fact, recognize that "it *may* be necessary for a submitter to include clinical or other scientific information…" (emphasis added). This statement suggests that it will not always be necessary for this information to be provided. Applying this requirement automatically to all Class II devices and those Class I devices on the reserve list is excessive and suggestive of current PMA requirements (potentially eroding the distinctions between 510(k) and PMA).

AdvaMed is concerned that the Working Group proposal requests not only information that the 510(k) sponsor knows, but also all scientific information regarding the safety and/or effectiveness that "should be reasonably known" to the sponsor. This reflects the PMA standard for information on safety and effectiveness, not the 510(k) standard for showing substantial equivalence. This standard departs from the substantial equivalence determination established by law in Section 513(i) of the Act by implying that a full review of safety and effectiveness would be required. In addition, the language is too vague for industry to provide a consistent set of information to CDRH in any given 510(k) filing. Without a clear and reasonable definition of CDRH expectations, the 510(k) sponsor would not know whether they have met the requirement until they receive feedback under the 510(k) process from CDRH. The 510(k) sponsor also would be limited in the amount of information available for a predicate device that was not their own design.

In addition, routine submission of both a listing and a description of all scientific information for all 510(k)s would be burdensome on both industry and CDRH, with unclear benefit. As discussed elsewhere within these comments, Least Burdensome requirements do apply to 510(k) submissions and should be applied to this specific recommendation.

The example CDRH provides in its report for the need for all scientific information indicates a situation where a submitter omitted data from three clinical studies that contradicted the studies submitted in support of the 510(k). Requiring submission of all scientific information for all 510(k)s is an excessive remedy that is poorly tailored to the example proffered. In fact, this example is adequately covered by the Truthful and Accurate Statement that companies are required to sign with each 510(k) submission. Most companies understand well the implications

of submitting a false statement of truthfulness and accuracy and are quite diligent at assuring that the totality of information submitted in a 510(k) accurately represents the safety and effectiveness of the new device. One must assume that, in an extreme situation like the one depicted by FDA, where a company knowingly excludes information that is relevant to substantial equivalence and directly contradictory to the data submitted in the 510(k), FDA will take action against the company based on its failure to meet the requirements of the Truthful and Accurate Statement.

A final consideration for CDRH is whether a requirement for all scientific information could be implemented without statutory change. AdvaMed recognizes that FDA may request any information regarding safety and effectiveness about a device under review when that information is necessary to make the substantial equivalence determination (21C.F.R. § 807.87(1). However, it is not clear whether, *a priori*, "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" meets this test and is necessary to the substantial equivalence determination of all 510(k)s. Therefore, AdvaMed believes that implementation of this as a pre-stated requirement for all devices would require a statutory change.

Type and Level of Evidence Needed

Recommendation: *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.*

AdvaMed does not support the recommendation to identify a subset of Class II devices called "Class IIb." While AdvaMed supports strengthening the 510(k) process by providing enhanced transparency and predictability to the CDRH reviewer expectations for a small, focused subset of Class II devices, we are concerned that the scope of the products proposed by FDA is too broad and the proposed requirements, when considered in their totality, are overly and unduly burdensome for Class II devices.[12] AdvaMed submitted its own proposal for a small focused subset of Class II devices to the docket (see Attachment C). We would like to re-emphasize that our proposal was not meant to, nor do we expect it will, create a new classification scheme for medical devices in the United States, but rather creates an informal, small, focused subset of Class II device types for which CDRH has provided advanced notice that additional information beyond that normally provided in a 510(k) may be expected to support a substantial equivalence determination. It is important to note that the AdvaMed proposal provided suggestions for a number of additional submission requirements that could be required for a device in the subset; it did not recommend that all devices in the subset be required to comply with all enhanced requirements. Nor did it suggest that all devices for which CDRH currently requires clinical information automatically become members of the subset.

[12] In its August 31, 2010 webinar the Agency conveyed that all devices for which FDA requests clinical data would be included in Class IIb.

Therefore, as this proposal is further developed, we urge CDRH to focus the AdvaMed's proposal for "a subset of Class II" and a consideration of a risk-based guidance for evidentiary standards for specific device types. This shift would make clear that this is not a new classification scheme, but simply a risk-based guidance that provides clearer direction for submissions for certain device types within the current Class II program. Because these appropriately identified devices will require additional resources by both industry and FDA, it is important that they are limited to a small number of higher risk devices where public safety will benefit from the extra expenditure of resources, otherwise the extra requirements will not be practically implementable and will detract from the focus on the truly higher risk devices.

AdvaMed believes that its proposed special controls for a small subset of Class II devices provides an opportunity to consider the down-classification of certain Class III devices with a proven track record of safety and effectiveness. The special controls would allow the Agency to establish any additional pre- and postmarket requirements that may be deemed necessary for such down-classified devices.

For any subset of Class II devices, it is necessary to define clear criteria and standards that apply, through a public notice and comment period, for determining which device types fall within this higher risk subset. The types of devices that would fall into this subset would be determined based on risk management processes, and could include certain 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. However, permanent implants, life-sustaining devices, and life-supporting devices with a record of safety in clinical use or with up-to-date standards, guidance and/or special controls that have proven effective would **not** warrant placement in the higher risk subset.

We disagree with OIVD's recent public comment that all Class II *in vitro* diagnostic devices for which clinical data are required should be in the higher risk subset of Class II.[13] While the regulations at 21 C.F.R. § 809.10 provide for performance data, CDRH interprets this, in many cases, to mean clinical data comparing IVD performance to whatever OIVD determines to be the "gold standard." There is little evidence to suggest that the current 510(k) contents fail to provide sufficient information to enable OIVD to clear safe and effective devices. If, in fact, any IVDs are to be a part of this subgroup, the decision should be risk based, consistent with the principles of AdvaMed's *Risk-Based Approach for the Regulation of All Diagnostics*, and be supported by evidence of significant issues with an entire category of products.

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[13] See transcript of August 31, 2010 CDRH webinar on 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.

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

AdvaMed does not support the recommendation to create a Class IIa and a Class IIb. AdvaMed agrees that training for review staff and industry is essential in providing safe and effective products to patients, however we disagree with the name and the concept of Class IIa and Class IIb. The names imply a new classification structure that exceeds the current statutory authority of the Agency. If a guidance for a small Class II subset of devices is developed, it must be made clear to both the review staff and industry that this is not considered device reclassification or creation of a new classification scheme. Once the criteria and process for a "small subset of Class II" is developed and is subject to notice and comment, AdvaMed encourages training of review staff and industry on the application and implementation of relevant guidances.

Clinical Information

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

AdvaMed does not agree with FDA's premise of a Class IIb designation. AdvaMed agrees that CDRH should provide greater clarity regarding the circumstances in which it will request clinical information in support of a 510(k), and what type and level of clinical information is adequate to support clearance. Although not explicitly identified by the 510(k) Working Group as an issue, AdvaMed believes that greater clarity is needed in distinguishing clinical information intended to support 510(k) clearance from clinical information supporting PMAs.

Examples of clinical information that may be used to support substantial equivalence may consist of 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, or results of pre- and postmarket investigation(s) of the device.

As part of the larger regulatory picture, the 510(k) submission process assures safety and effectiveness by demonstrating substantial equivalence and documenting critical aspects of

device performance and mitigating risks. If Congress intended for the 510(k) process to assure safety and effectiveness in absolute terms (rather than through a comparative lens), then both the regulatory and resource requirements under this section of the Act would need to change as would resources to accompany such expectations. CDRH should keep in mind that most devices have a long history of safe and effective use that precludes the need for clinical data or clinical evidence.

In the context of a "subset of Class II" submission, AdvaMed supports this recommendation for those devices in the subset that require clinical information to establish substantial equivalence. However, AdvaMed does not support the concept that all IVD devices for which the Office of In Vitro Diagnostics has historically requested clinical data, should be placed in the subset of Class II devices. For many IVD devices, performance information, as specified in 21 C.F.R. § 809.10, is sufficient to establish substantial equivalence. The requirement for clinical data should only apply to those IVD devices that require clinical data to establish substantial equivalence because there is no acceptable comparator or because the test or technology is new and it is not possible to tie the results to a clinical condition or diagnosis.

AdvaMed supports the recommendation that CDRH define the term "clinical data." AdvaMed recommends that CDRH review the definitions for "clinical evidence", "clinical data" and "clinical evaluation" provided in the GHTF document "Clinical Evidence-Key Definitions and Concepts" (SG5/NIR8:2007). Harmonization with these definitions would foster a common understanding among not only CDRH review staff and industry but also with international regulatory agencies

Postmarket Information

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

AdvaMed does not support this 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 require postmarket studies as part of premarket special controls and through Section 522 postmarket surveillance orders, further authority is unnecessary and may lead to a proliferation of burdensome postmarket studies that add little to enhance public health.

AdvaMed supports the recommendation with modifications to explore greater use of CDRH's existing postmarket authorities for a subset of Class II devices. Under existing authorities, FDA can issue orders for post-market data through Section 522 of the Act, and in the case of special controls, under Section 513(a)(1)(B) of the Act, can require postmarket data through performance standards, postmarket surveillance, and patient registries.

Recommendation: *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.*

AdvaMed 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 timeframe. 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 do not support exploring how data collected or associated with UDI may be used as part of the 510(k) process, as it is premature at this time, and recommend CDRH defer evaluation of this option until such time as UDI is effective.

Manufacturing Process Information

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

AdvaMed supports this recommendation for only a small number of specific device types within the subset of Class II devices for which particular circumstances or conditions would require the submission of a summary of manufacturing information (e.g., manufacturing includes a unique process that is critical to the safety or efficacy of the device). Further, rather than submitting the level of detail required for PMA submissions, CDRH should clarify via guidance that only a summary (e.g., flow chart) of the manufacturing information relevant to safety and effectiveness of a device is required.

AdvaMed does not support manufacturing information being provided for any *in vitro* diagnostic device in Class II. Although in its report, CDRH indicates this requirement is appropriate for any product with lot-to-lot variability, it typically is not the manufacturing process that introduces variability.

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

AdvaMed supports the recommendation to clarify when it is appropriate for CDRH to use its current authority.

There would be no benefit to the public health from withholding substantial equivalence determinations for a subset of Class II devices, or any devices, because of alleged failures to comply with good manufacturing practice requirements (GMPs) unless there is a substantial likelihood that the failure to comply with GMPs will potentially present a serious risk to human health. Section 513(f)(5) in FDAMA was enacted in response to FDA's extra-legal creation and use of the "reference list," to withhold 510(k) clearances until FDA verified that alleged GMP violations identified in inspections were corrected. In response to this program, Congress was "concern[ed] that FDA was inappropriately using the device premarket notification process for compliance purposes."[14] "This process was unfair and denied device manufacturers an opportunity to dispute effectively FDA's allegations that firms were not in GMP compliance. FDA set itself up as judge and jury and, in essence, administratively enjoined the classification of devices . . . ."[15]

The reference list unjustifiably delayed 510(k) clearances until alleged GMP violations were remedied and the Agency re-inspected the facility to confirm remediation. This led to significant delays in substantial equivalence determinations, resulting in physicians and patients being denied the availability of new devices.[16] More importantly, GMP corrections had nothing to do with a determination of substantial equivalence (classification of a medical device). Simply put, devices were withheld from the public, in most instances, without any actual health justification.

In eliminating the reference list, Congress maintained a link between GMPs and 510(k) by permitting the withholding of substantial equivalence determinations where a non-compliance presented "a substantial likelihood that the failure to comply with [GMPs] will potentially present a serious risk to human health."[17] In other words, Congress believed that more harm would be done to the public health by withholding the initial classifications of devices than letting them go forward, unless a significant health harm related to a GMP violation was likely.

The Agency is vested with substantial enforcement authorities to ensure compliance with its laws and can prohibit the distribution of adulterated or misbranded devices. To force enforcement considerations into the premarket context would delay the entire premarket review process without a net benefit to the public. The 510(k) process is one of classification and comparison to a legally marketed device. It is not an evaluation of whether a company is in compliance with the Act, nor should it be. Indeed, the legislative history of Section 513(f)(5) states that "[c]learly, FDA has substantial authority to enforce the Act against illegal devices and the

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14 Senate Report No. 105-43, 105th Cong. 1st Sess., at 29.

15 *Id.*

16 *See id.* (stating, "[o]ver the past five years, the FDA has withheld device classification determinations of substantial equivalence because of its belief that firms were not in compliance with good manufacturing practices.").

17 *See* § 513(f)(5).

persons who market them. It is unacceptable that the Agency misuse premarket notification to avoid enforcing the Act."[18]

A substantial equivalence determination does not void or otherwise limit FDA exercise of its enforcement authorities under the Act nor does it empower recipients of substantial equivalence orders to introduce into commerce misbranded or adulterated devices. Congress explained that:

> FDA can find a device substantially equivalent to a predicate device and still inform the device manufacturer that . . . it should not be marketed because of the Agency's view that the device does not comply with the law in some specified respect. Then, if a person markets the device after such notice, FDA can enforce the Act.[19]

The Act describes a complete regulatory regime that includes premarket review processes and substantial authority to remove violative devices from the market, especially including those that present potential harm to the public health. Congress was fully aware of the immense authority it vested in the FDA to maintain the Congressional balance of not over-regulating devices in the premarket context, while ensuring that only safe and effective devices can be introduced into commercial distribution.

AdvaMed recommends that if the Agency determines that a substantial equivalence determination should be withheld because a GMP non-compliance presents "a substantial likelihood that the failure to comply with [GMPs] will potentially present a serious risk to human health," the target company be afforded the due process opportunity to discuss the decision with the Agency prior to the Agency taking action.

AdvaMed does not support pre-clearance inspections for the device types in the subset of Class II devices or any Class II devices. Section 510(k) is a classification provision and not an approval authority. As such, and unlike PMA safety and effectiveness determinations, pre-clearance inspections have no relevance to the substantial equivalence question.

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

Product Codes

Recommendation: *The 510(k) Working Group recommends that CDRH develop guidance and Standard Operating Procedures (SOPs) on the development and assignment of product codes, in*

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18 *Id.*

19 *Id.*

order to standardize these processes and to better address the information management needs of the Center's staff and external constituencies.

AdvaMed supports this recommendation. AdvaMed also recommends that CDRH include a process for alerting the public (industry) when new product codes are established.

Recommendation: *510(k) Working Group further recommends that CDRH enhance existing staff training on the development and assignment of product codes.*

AdvaMed supports enhanced staff training on the development and assignment of product codes.

510(k) Databases

Limited Tools for Review Staff and Outside Parties

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

AdvaMed agrees that CDRH should develop an easily searchable database that provides appropriate information to the public. AdvaMed agrees that the database should include a verified 510(k) summary. Although it was not specifically stated in the 510(k) Working Group Recommendations, the value of a reviewer "decision summary" was discussed in the text of the report. AdvaMed agrees with CDRH comments that "publicly providing accurate and meaningful information about previous 510(k) decisions and predicate devices is essential to increasing the transparency and predictability of CDRH's 510(k) decision making." We also agree with CDRH's position that providing information about the basis for previous decisions can provide much-needed clarity about CDRH's evidentiary expectations and decision-making rationale. The decision summaries currently posted by the OIVD for IVD clearances have proven to be a valuable tool to industry. The decision summary, in combination with consistent, verified 510(k) submission summaries, would provide interested parties, including FDA reviewers, third party reviewers, clinicians, and industry with meaningful information about the subject of the 510(k) submission and the predicate device(s). A decision summary would improve consistency in 510(k) decision-making among reviewers, and when updated guidance is lacking, enable manufacturers to understand current clearance requirements for their device.

It should be noted that AdvaMed recommends eliminating the option for submitters to provide a 510(k) Statement in lieu of a 510(k) summary. This change will assure that consistent and high quality information about any new or modified 510(k) device will be readily available to the public.

AdvaMed does not, however, support the posting of photographs, schematics, and other graphic depictions of devices on the searchable database. Schematics are proprietary information and should not be posted in a publicly-searchable database. Further, photographs and other depictions submitted with the 510(k) for the purpose of establishing substantial equivalence and educating the reviewer may be cosmetically different than the marketed device, thereby causing confusion for the public. Foreign competitors may use this information to produce counterfeit devices or to shorten device development times and speed their time to market, resulting in competitive harm to U.S. companies. Competitive advantages afforded to foreign and domestic competitors would exist even when actual proprietary information is not disclosed.

Recommendation: *The 510(k) Working Group recommends that CDRH develop guidance and SOPs for the development of 510(k) summaries to assure they are accurate and include all required information identified in 21 CFR 807.92. The Center should consider developing a standardized electronic template for 510(k) summaries.*

AdvaMed supports CDRH's development of guidance and SOPs for 510(k) summaries. In fact, in its March 19, 2010 comments to Docket No. FDA-2010-N-0054, AdvaMed recommended that FDA establish guidance to augment its regulations regarding 510(k) Summary content and ensure compliance with the requirements. We also recommended that FDA consider providing a template, to assure that the quality of information in 510(k) Summaries is consistent and complete. This template will provide information that will help companies to determine whether a particular device can be used as a predicate, as well as assisting companies in determining the data and other information they will need to include in their own 510(k)s. AdvaMed is developing a standardized format and template for 510(k) summaries, which we will be pleased to provide to CDRH for its consideration and use.

Lack of Ready Access to Final Device Labeling

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

IIb" device subset described above, or with a particular section of labeling. CDRH should also consider posting on its public 510(k) database the version of the labeling cleared with each submission as "preliminary labeling," in order to provide this information even before the Center has received and screened final labeling.

AdvaMed does not support this recommendation. AdvaMed believes that the Working Group's assumption of benefits to medical professionals and device users are overstated. Collection, organization, editorial checks of redlined copy, and posting in a database by CDRH review staff will require a significant investment of resources (both human and technological) without meaningful benefit to the public health. Labeling of some devices contains information that is intended for hospitals or practitioners. Public misuse or confusion may result, if such labeling is broadly available to the public (such as how to program some electrical devices). Public posting of preliminary labeling would provide undue benefit to competitors and would inhibit U.S. innovation. AdvaMed strongly feels that dissemination of labeling to patients (direct when appropriate or through the attending clinician) and to clinicians should remain the responsibility of the manufacturer, thereby ensuring the information reaches the appropriate audience and does not cause confusion. When it is determined appropriate by a manufacturer, labeling information is provided on a manufacturer's website and is controlled by the manufacturer to maintain accurate up-to-date labeling, and if necessary, lot-specific labeling (e.g., certain IVD products).

Limited Information on Current 510(k) Ownership

Recommendation: *The 510(k) Working Group recommends that CDRH develop guidance and regulations regarding appropriate documentation of transfers of 510(k) ownership. The Center should update its 510(k) database in a timely manner when a transfer of ownership occurs.*

AdvaMed supports this recommendation and believes that the complete history of 510(k) ownership should be maintained. We believe that it will be helpful not only for the U.S., but also for U.S.-registered foreign devices. It also would be valuable for CDRH to show the full chain of 510(k) ownership.

We urge FDA to follow through on this recommendation. We also suggest that, if possible, implementation should be handled through an existing and familiar process such as registration and listing. Implementing the recommendation in this manner would place the information in an existing database, and would simplify both FDA's entry of the information and the public's access to the information.

AdvaMed
Advanced Medical Technology Association

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.*

Reviewer Expertise and Experience

Recommendation: *The 510(k) Working Group recommends that CDRH continue to take steps to enhance recruitment, retention, training, and professional development of review staff, including providing opportunities for staff to stay abreast of recent scientific developments and new technologies. This should include increased engagement with outside experts, as discussed further in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making (described further in Section 2, below).*

AdvaMed supports this recommendation. AdvaMed agrees that CDRH should continue efforts to enhance recruitment, retention, training, and development of review staff. AdvaMed agrees with the approach noted multiple times in the recommendations that proper development and delivery of appropriate training is key to the success of any organization and to successful implementation of any change. We also agree that well-designed and effectively delivered training will lead to the greatest likelihood of program success and should be directed at both CDRH staff and industry.

In addition, AdvaMed offers the following suggestions as FDA explores opportunities to enhance its training program. We believe that the "train the trainer" approach works well for adult education and that there are several groups that FDA should consider utilizing in this way. External experts from academia and FDA alumni should be considered as potential partners to fill the training needs that will result from the changes being proposed to the 510(k) program. The use of outside experts and a "train the trainer" approach will minimize the amount of CDRH managers' time needed to perform the number of training sessions that will be required to accomplish these changes.

AdvaMed recommends that staff training require testing or proof of proficiency, similar to the requirements for training industry personnel described in Quality System Regulation. We also believe that this training should be required before staff is empowered to perform reviews or assessments under any new procedures. This training would parallel industry training requirements.

Lastly, we are in complete agreement that FDA Vendor Days and other ways to familiarize the staff with various technologies are an important addition to the program. Site visits to industry should be expanded and site visits to academia should be added to the current programs. We support fully the idea that more engagement with scientific experts from all over the world would be a benefit to FDA as well as to industry.

Recommendation: *The 510(k) Working Group further recommends that CDRH consider establishing a Center Science Council comprised of experienced reviewers and managers and under the direction of the Deputy Center Director for Science. The Science Council should serve as a cross-cutting oversight body that can facilitate knowledge-sharing across review branches, divisions, and offices, consistent with CDRH's other ongoing efforts to improve internal communication and integration. The Science Council's role in improving the consistency of Center decisions is discussed in greater detail in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making.*

AdvaMed supports the establishment of a Center Science Council comprising 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.

To enhance the value the Council can provide, the Agency should ensure that the Council provides oversight to assure consistency and integrity of the 510(k) process, rather than engaging in routine decisions that may have the unfortunate effect of undermining the process. Further, the Council should not have the authority to reverse decisions.

This process for managing new scientific information **should not be used to reach recommendations applicable to individual devices without input from the entity with legal authority to market the device**. It should not replace any legally required processes such as the current consultative and appeals routes, or otherwise render these processes superfluous to substantive outcomes. The Center Science Council should be trained to understand FDA's legal authorities and processes, in order to assure that the Council focuses appropriately on "regulatory science" rather than "pure science" in providing Center oversight.

Third Party Review

Recommendation: *The 510(k) Working Group recommends that CDRH develop a process for regularly evaluating the list of device types eligible for third-party review and adding or removing device types as appropriate based on available information. 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.*

AdvaMed does not support the recommendation to limit eligibility for Third Party review as stated. As noted in CDRH's 510(k) Working Group Preliminary Report and Recommendations, Third Party Reviews were established under FDAMA. Medical devices are eligible for Third Party Review except as prohibited in Section 523(a)(3) of the Act, where it states, "An Accredited person may not be used to perform a review of – (i) a Class III device; (ii) a Class II

device which is intended to be permanently implantable or life sustaining or life supporting; or (iii) a Class II device which required clinical data in the report submitted under Section 510(k) for the device." The current law has no other eligibility requirements, such as device-specific guidance documents, or other imposed criteria.

The purpose of the Accredited Persons Program (AKA Third Party Review) is to implement Section 523 of the Act by accrediting third parties to conduct the initial review of 510(k)s for selected low-to-moderate risk devices. The Accredited Persons Program was intended to enable FDA to use its scientific review resources for higher-risk devices, while maintaining a high degree of confidence in the review of low-to-moderate risk devices by Accredited Persons, and to provide manufacturers of eligible devices an alternative review process that may yield more rapid 510(k) decisions.

Recommendation: *The 510(k) Working Group further recommends CDRH enhance its third-party reviewer training program and consider options for sharing more information about previous decisions with third-party reviewers, in order to assure greater consistency between in-house and third-party reviews.*

AdvaMed supports this recommendation. AdvaMed supports CDRH enhancing its third-party reviewer training program; we also recommend periodic retraining and auditing of third party reviewers.

While the 510(k) Report referenced quality issues with the Third Party Review program, it is important to note that the report cited an analysis of third party reviews during the last 9 months of 2005, a very small and potentially outdated sample of the program as it exists today.

Seven percent of 510(k)s, or in excess of one thousand 510(k)s submitted to CDRH over the last 5 years were reviewed by Third Parties, illustrating that the program remains important to both industry and the Agency, and that it should be preserved and improved as necessary. The Accredited Persons program provides a pool of trained and qualified resources, assisting the Agency in the review of 510(k)s, and in some ways, acting in the capacity of the Ad Hoc review team as noted within the 510(k) Report.

The medical device industry values the Third Party review process as described in the law, and as currently implemented by CDRH. As requested by Dr. Shuren in the Forward of the 510(k) report, AdvaMed recommends the following 'potential alternatives' for improving the program rather than reducing the devices eligible for Third Party Review:

- The 510(k) report states, "Concerns have also been raised about the level of training and experience of accredited third parties. CDRH offers training for third-party reviewers, but it is only offered every 3-4 years." FDA assessment, accreditation, and training of Accredited Persons should occur not only upon acceptance of an Accredited Party into the program, but on an ongoing, periodic basis, thereby ensuring continued qualification of the Third Party review organizations.

- FDA should periodically audit the personnel qualifications for Accredited Persons, to ensure they are equivalent to the level within the CDRH's Office of Device Evaluation.

- FDA should periodically audit each Accredited Person to ensure performance and to inspect records, correspondence, and other materials relating to Accredited Person to ensure the quality of the reviews.

- In accordance with Section 523(b)(2) of the Act, FDA may suspend or withdraw accreditation from a Third Party, after providing notice and an opportunity for an informal hearing, when a Third Party:
  1) is not substantially in compliance with Section 523;
  2) fails to act in a manner consistent with the purposes of Section 523; or
  3) poses a threat to public health.

- FDA should educate and enforce the requirement that it is a prohibited act under Section 301(y)(1) for an Accredited Person, to:
-
  1) submit a report that is false or misleading;
  2) disclose confidential information or trade secrets without the submitter's consent; or
  3) receive bribes or perform a corrupt act.

- The 510(k) Working Group notes that Third Parties lack access to predicate information and to new postmarket safety information, and they find it challenging to keep up with CDRH's evolving evidentiary expectation in the absence of device specific guidance. Prior to initiating a 510(k) review, the Accredited Person should contact the appropriate CDRH Office of Device Evaluation (ODE) Branch Chief (or designee) to identify pertinent issues and review criteria, obtain non-confidential predicate information such as the reviewers' decision summary for the predicate device(s), and discuss any new postmarket safety information related to this type of device. In this way, the Accredited Person will be able to stay abreast of CDRH's evolving evidentiary expectations. Posting of 510(k) summaries on a public database also will assist in keeping Accredited Persons current on evidentiary expectations.

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

Recommendation: *The 510(k) Working Group recommends that CDRH 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.*

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AdvaMed endorses the idea of developing a set of metrics to assure continuous quality assurance of the 510(k) review program. We believe that metrics carefully designed to evaluate specific aspects of the program will provide clear guidance to the Agency for maintaining and improving the effectiveness of the program.

Each metric should be focused on a specific question or aspect of the program. Collectively and individually, the metrics need to be simple and unambiguous both to FDA staff and to other stakeholders. The metrics must be pursued diligently, and the results should be made public in a timely manner.

Finally, should FDA develop a recommendation or proposal to modify the system based on the results shown by one or more of the metrics, FDA will need to demonstrate clearly the causal relationship between the recommendation and the metric. In other words, changes that FDA proposes should be traceable to results of the metrics that they establish.

Recommendation: *The 510(k) Working Group further recommends that CDRH 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.*

AdvaMed is encouraged by CDRH's intent to assess the effectiveness of the review process, and to drive greater knowledge and consistency among reviewers. These periodic audits of review decisions should not be punitive and should be for the purpose of assessing the review process and ensuring consistency across the Agency, not putting the Science Council in the position of reversing earlier decisions. For that reason, if CDRH moves forward with such audits, it will be critical for CDRH to clearly define objective audit criteria and the authority of the Council and to share those criteria with staff and industry. CDRH and industry need to have the same understanding of expectations for the 510(k) program to be effective. In addition, if CDRH conducts such audits, 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.

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VOLUME II-UTILIZATION OF SCIENCE IN REGULATORY DECISION MAKING

General Comments

As a science-based agency, FDA is charged with basing its decisions on valid scientific information. However, information is not science simply because it is used in decision making. Science involves the testing of hypotheses and the repeatability of experiments, not simply the collection of unverified information. While some anecdotal or new information may be true and useful, much of it will not meet standard criteria for science and may require confirmatory studies.

Specific Comments

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.*

Premarket Review

Interpretation of the "Least Burdensome" Provisions

Recommendation: *The 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 (21 USC § 360c(a)(3)(D)(ii) and 21 USC §360c(i)(1)(D)). CDRH should clearly and consistently communicate that, while the "least burdensome provisions" are, appropriately, meant to eliminate unjustified burdens on industry, such as limiting premarket information requests to those that are necessary to demonstrate reasonable assurance of safety and effectiveness or substantial equivalence, they are not intended to excuse industry from pertinent regulatory obligations nor to lower the Agency's expectations with respect to what is necessary to demonstrate that a device meets the relevant statutory standard.*

AdvaMed does not support the recommendation to revise the current Least Burdensome guidance document. The Report (page 17) notes that the staff at FDA are concerned about their ability to require companies to submit additional data in their 510(k)s when those data have not traditionally been required for similar products. The fact that companies raise the "least burdensome" requirement of the law as a defense against complying with such requests or as a basis for complaints to the Ombudsman does not mean that the section of the law or the guidance developed in 2002 by CDRH are inadequate. AdvaMed agrees with the FDA's characterization of this provision that the "...goal was to streamline the regulatory process (i.e., reduce burden) to improve patient access to breakthrough technologies" "…not lower the statutory criteria for determination of substantial equivalence."

The provisions of the Act are clear:

Section 513(a)(3)(D)(ii)
"Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as a result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval."

Section 513(i)(1)(D)
"Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such requests, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly."

It appears that the principal issue is the need for education and training of industry and CDRH staff to improve their understanding of the meaning and intent of the least burdensome provision.

Education and training of industry and staff of the least burdensome principles are appropriate steps. As noted in the report, the background of FDA' 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 applications." The report further notes, "[t]hese principles are consistent with good governance in general." 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 and should be implemented and evaluated prior to any revision of this guidance.

FDA should communicate clearly and consistently that the least burdensome provision is meant to eliminate unjustified burdens on industry. The Agency also should emphasize that the provisions are not intended to lower the Agency's expectations with respect to what is necessary to demonstrate that a device meets the relevant statutory standard.

"Least Burdensome" is a valuable concept for not only FDA processes, but for all government regulation. In fact, the current administration has recently issued a request to all agencies asking them to work in a least burdensome fashion. Executive Order 12866 directs agencies "to foster the development of effective, innovative, and least burdensome regulations" (Section 6(a)(2)), and to "identify and assess available alternatives to direct regulation, including . . . providing

information upon which choices can be made by the public" (Section 1(b)(3)). Executive Order 12866 also directs agencies to analyze "potentially effective and reasonably feasible alternatives to the planned regulation, identified by the agencies or the public (including improving the current regulation and reasonably viable nonregulatory actions)" (Section 6(a)(3)(C)(iii)).

Quality of Clinical Data

Recommendation: *The Task Force recommends that CDRH continue its ongoing efforts to improve the quality of the design and performance of clinical trials used to support premarket approval applications (PMAs), in part by developing guidance on the design of clinical trials that support PMAs and establishing an internal team of clinical trial experts who can provide support and advice to other CDRH staff, as well as to prospective investigational device exemption (IDE) applicants as they design their clinical trials. The Center should work to assure that this team is comprised of individuals with optimal expertise to address the various aspects of clinical trial design, such as expertise in biostatistics or particular medical specialty areas. The team would be a subset of the Center Science Council discussed in Section 4.2.1 of this report, and, as such, it may also serve in the capacity of a review board when there are differences of opinion about appropriate clinical trial design and help assure proper application of the least burdensome principle. CDRH should also continue to engage in the development of domestic and international consensus standards, which, when recognized by FDA, could help establish basic guidelines for clinical trial design, performance, and reporting. In addition, CDRH should consider expanding its ongoing efforts related to clinical trials that support PMAs, to include clinical trials that support 510(k)s.*

AdvaMed supports the development of guidance on the design of clinical trials for support of PMAs and, when necessary, 510(k)s. This guidance should address the wide range of clinical trial designs and not be limited only to randomized controlled trials. AdvaMed strongly recommends that CDRH include industry in the guidance development process thus allowing valuable input from experienced and knowledgeable industry clinical staff.

AdvaMed supports CDRH's establishment of an internal team of clinical trial experts who can provide support and advice to FDA staff as well as prospective investigational device exemption (IDE) applicants.

AdvaMed also strongly supports CDRH's involvement with the development of domestic and international consensus standards that would be recognized by FDA and provide harmonization of requirements.

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

submission interactions between industry and Center staff to supplement available guidance on pre-IDE meetings.

AdvaMed supports this recommendation. AdvaMed supports efforts to improve the IDE decision making process including the evaluation and possible enhancement of interactions with industry. AdvaMed has previously submitted to FDA (April 18, 2009) an analysis of existing pre-submission meetings and recommendations for best practices as it relates to these meetings for the life-cycle of product development and approval. AdvaMed would welcome an opportunity to work with CDRH to maximize the efficiency and quality of the IDE review and decision making process.

Review Workload

Recommendation: *The Task Force recommends that CDRH consider creating a standardized mechanism whereby review Offices could rapidly assemble an ad hoc team of experienced review staff from multiple divisions to temporarily assist with time-critical work in a particular product area, as needed, in order to accommodate unexpected surges in workload. This would need to be done in such a way that ad hoc teams would only assist with work that does not require specialized subject matter expertise beyond what the team members possess. The Task Force recognizes that such an approach is only a stop-gap solution to current workload challenges, and that additional staff will be necessary to better accommodate high workloads in the long term. The Center's staffing needs are discussed further below.*

AdvaMed is pleased that FDA is addressing its capacity to respond to surges in review workload in a standardized way. CDRH has in the past drawn on knowledge and expertise from across the Center to address time-critical work or work that required a specific expertise that resided in select individuals. The process, however, was not consistent. Having a more formal process to address such needs will make the review process more predictable across review divisions. This would be particularly useful when there are potentially competing needs from different review groups.

There are four recommendations that we would like to make as this process is developed. The first is that the Agency develops a method to assure the appropriate needs and skills are identified up front. As noted in the report, this is necessary to assure that the work being requested of an *ad hoc* team is within their skill set. It is important to ensure that members of the team are adequately trained and have sufficient knowledge of the technologies and issues related to the particular devices being reviewed. The second recommendation is that the *ad hoc* team includes at least one member from the relevant reviewing branch. The third recommendation is that there is a mechanism for oversight of the work of such teams separate from the proposed review of routine reviews. We believe this is necessary to assure the consistency of review work within branches no matter who is performing the reviews and to provide a mechanism to evaluate the impact of the broader and more formal program in this arena. Lastly, we believe it is important that the creation of an *ad hoc* team to address time-critical work does not adversely

affect routine review work, especially in the review divisions from which the members of the *ad hoc* review team were selected.

Recommendation: *The Task Force recommends that CDRH 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.*

AdvaMed believes that expending valuable Center resources to evaluate the sources of challenge for Center staff in complying with the mandatory 30-day timeframe is unnecessary. We believe that with appropriate guidance for pre-IDE meetings and with well-managed and productive pre-IDE meetings, Center staff will accommodate the 30-day timeframe. AdvaMed would welcome an opportunity to work with the Center to mitigate the challenges and increase process efficiency and quality.

Postmarket Oversight

Recommendation: *The Task Force recommends that CDRH continue ongoing efforts to develop better data sources, methods, and tools for collecting and analyzing meaningful postmarket information, consistent with the Center's FY 2010 Strategic Priorities. In addition, the Center should conduct a data gap analysis and a survey of existing U.S. and international data sources that may address these gaps. These efforts should be in sync with and leverage larger national efforts. As CDRH continues its efforts to develop better data sources, methods, and tools, it should invite industry and other external constituencies to collaborate in their development and to voluntarily provide data about marketed devices that would supplement the Center's current knowledge.*

AdvaMed supports efforts to develop additional data sources. However, continued validation of data owners, research contractors, study methods, and data sets are necessary. Criteria for the selection of data sources should be established. Data owners, research contractors, study methodologies, and data sets should be evaluated and validated for accuracy, relevancy and quality. With respect to relevance, it will be important to validate in advance which data sets are capable of answering which types of queries to ensure that inappropriate queries are not sent to data owners which could potentially result in invalid responses. There should be a periodic auditing process to ensure the continued validity of the methodologies and data sets.

Recommendation: *The Task Force recommends that CDRH conduct an assessment of its staffing needs to accomplish its mission-critical functions. The Center should also work to determine what staff it will need to accommodate the anticipated scientific challenges of the future. CDRH should also take steps to enhance employee training and professional development to assure that current staff can perform their work at an optimal level. As part of this process, the Center should consider making greater use of professional development opportunities such as site visits or other means of engagement with outside experts in a variety of areas, including clinical care, as described below. This recommendation complements the*

Center's ongoing efforts under its FY 2010 Strategic Priorities to enhance the recruitment, retention, and development of high-quality employees.

AdvaMed supports this recommendation. AdvaMed encourages CDRH to determine essential functions that support the FDA priorities of protecting public health and access to improved medical treatment and focus resources on these functions. Recruitment and training and professional development of highly qualified and motivated employees are essential to achieve CDRH goals. AdvaMed supports CDRH making greater use of site visits, including industry site visits.

Recommendation: *The Task Force recommends that CDRH continue the integration and knowledge management efforts that are currently underway as part of the Center's FY 2010 Strategic Priorities. As part of these efforts, the Task Force recommends that CDRH develop more effective mechanisms for cataloguing the Center's internal expertise, assess the effectiveness of the inter-Office/Center consult process, and enhance the infrastructure and tools used to provide meaningful, up-to-date information about a given device or group of devices to Center staff in a readily comprehensible format, to efficiently and effectively support their day-to-day work.*

AdvaMed supports this recommendation. It is essential that CDRH have the tools and infrastructure necessary to allow reviewers to access relevant internal expertise and have meaningful, up-to-date information about devices (e.g., via a 510(k) summary database).

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

Recommendation: *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.*

AdvaMed encourages FDA to establish access to a wide range of experts, including medical and diagnostic experts who understand the medicine and technology of devices. On page 8 of the Report, the Task Force expresses a finding that, "it is difficult for Center staff to tap meaningful external scientific expertise in a timely manner." The Report then recommends that FDA establish a web-based system to enable staff to interact effectively with appropriate external experts. This recommendation partially parallels a similar recommendation that AdvaMed made during the discussions of FDA's use of science in decision making and the review of the 510(k) process. Despite our belief that both FDA and industry will be well-served if FDA staff can consult with external experts, we have several concerns that can be addressed at the beginning of the process design.

The term "social media technology" is unclear to us. Social media have become an enticing Internet venue serving a variety of purposes, some positive, others negative. Social media sites also have exhibited significant security problems. While we do not believe that FDA plans to consult scientists using current, publicly-available sites, we do believe that FDA must define the goals and the parameters, especially the limits, of the anticipated interactions.

Clearly, if external experts are to be consulted on scientific issues during a product review, the consultation is likely to include a discussion of trade secrets, proprietary information, or both. FDA should establish a defined process for choosing and qualifying external experts and for ensuring that the interactions are properly scoped, limited, and balanced. FDA should ensure that input from external experts are documented in reviewer decision summaries. FDA also should ensure confidentiality of communications related to reviews. Therefore, it is vital that the system design requirements include both a high level of cyber security, secure user access controls and other administrative, technical, and physical safeguards to protect the confidentiality of the data and to prevent unauthorized use or access. These safeguards should provide the same level and scope of security as safeguards for other federal government information systems.[20] It will be both easier and less expensive to include these controls at the beginning of development as opposed to adding them along the way.

There also is concern about potential conflicts of interest. Conflict of interest applies not only to industry ties but also to academic interests and reputation. It is important to balance the vetting process to ensure a large pool of experts while also minimizing bias. The selection process for choosing external experts for the web-based network, and the names of external experts and their qualifications should be made available on the FDA website to add transparency to the process. Additionally, developing a process to ensure transparency to the sponsor when CDRH is consulting external experts is a necessary step.

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.*

Recommendation: *The Task Force 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 mechanisms, such as site visits, through which staff can meaningfully engage with and learn from experts in a variety of relevant areas, including*

[20] *See, for example*, Office of Management and Budget (OMB) Circular No. A-130, Appendix III--Security of Federal Automated Information Systems (http://www.whitehouse.gov/omb/circulars/a130/a130.html), Federal Information Processing Standard 200 "Minimum Security Requirements for Federal Information and Information Systems" (http://csrc.nist.gov/publications/fips/fips200/FIPS-200-final-march.pdf), and Special Publication 800-53 "Recommended Security Controls for Federal Information Systems" (http://csrc.nist.gov/publications/nistpubs/800-53-Rev2/sp800-53-rev2 final.pdf).

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.

AdvaMed supports this recommendation. AdvaMed member companies encourage visits by FDA to healthcare facilities where they may observe the use of medical devices and *in vitro* diagnostics by actual users of the devices.

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

There is a lack of clarity within and outside of CDRH about when new scientific information warrants certain types of action by the Center, particularly a change in premarket evidentiary standards.

Recommendation: *The Task Force recommends that CDRH 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. As it puts this approach into practice, CDRH should consider adopting several key principles. First, the process should allow for a range of individuals to participate in the deliberation phase, including managers and employees, to help take into consideration potentially cross-cutting issues and assure consistency in responding to new scientific information. To support this principle, CDRH should establish a Center Science Council, comprised of experienced employees and managers and under the direction of the Deputy Center Director for Science, to provide oversight and help assure consistency across the Center. Second, the process should be streamlined to allow for new information to be raised and addressed in a timely manner. Third, the process should include a mechanism for capturing in a structured manner the rationale for taking a particular course of action, so that it can be articulated clearly to staff and external constituencies and incorporated into the Center's institutional knowledge base. Fourth, the process should be designed to allow for prioritization of issues. The Center should also develop metrics to determine whether or not the new process is effective.*

It is essential that CDRH prospectively establish a process for determining what action, if any, should be taken when new information on product performance is made available. AdvaMed supports the development of the "Predictable Approach" framework for responding to new scientific information. The four basic steps, outlined by FDA, are an appropriate means of rationally and consistently managing new information that comes to light after products have been placed on the market. However, a critical first step is to assess whether the new information is scientifically valid or simply information that may not be verified or verifiable. Such assessments will govern what, if any, actions should be taken. We also agree with a key principle articulated by FDA, that the framework should allow for "a range of individuals to participate in the deliberation phase." It is imperative, however, that this range of individuals

includes representatives from industry that are the most knowledgeable in the design, manufacture, and distribution of the product in question. Similarly, it would be appropriate for the users of the product in question to be consulted during the deliberation phase.
Finally we concur that the framework should include a mechanism for capturing in a structured manner the rationale for taking a particular course of action, so that it can be articulated clearly to FDA staff and external constituencies and incorporated into the CDRH institutional knowledge base.

Recommendation: *The Task Force recommends that CDRH enhance its data sources, methods, and capabilities to support evidence synthesis and quantitative decision making as a long-term goal.*

AdvaMed supports this recommendation. CDRH must have the tools, knowledge and resources available to support their mission and goals.

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.*

Recommendation: *The Task Force recommends that CDRH continue its ongoing efforts to streamline its processes for developing guidance documents and regulation, consistent with the Center's FY 2010 Strategic Priorities. For example, CDRH should explore greater use of the "Level 1 – Immediately in Effect" option for guidance documents intended to address a public health concern or lessen the burden on industry. CDRH should also encourage industry and other constituencies to submit proposed guidance documents, which could help Center staff develop Agency guidance more quickly.*

AdvaMed supports the development of additional product specific guidance for FDA staff and industry. The increased issuance of Level 1-Immediately in Effect guidance, however, raises concerns about implementation of new expectations without adequate notice to affected stakeholders. In the real world of product submission development, there will be products in various stages of development, including submissions pending at the Agency, applications ready for submission to the Agency, and existing device trials near completion. There is a real need for notice and comment on guidance documents, and therefore the use of Level 1 guidance is best reserved for only those matters where there is an urgent and documented public health issue that must be immediately addressed. The gains in streamlining the Agency's guidance implementation process through increased issuance of Level 1-Immediately in Effect guidance seem to be modest and deny the full and rich exchange on information resulting from stakeholder involvement.

Additionally, there should be more extensive engagement in the development of guidance, such as placing FDA staff on joint teams with stakeholders, including industry, health care providers with product knowledge, and academic experts to develop first drafts of needed guidance.

Although guidance documents are not legally binding on the Agency, they do "represent the Agency's current thinking," 21 C.F.R. § 10.115(d)(3), and are relied upon by FDA review staff, device companies and other stakeholders. Because of the importance of these documents, the Agency would be better served if it were fully informed on the issues at hand, by receiving stakeholder and individual expert feedback, prior to publishing a draft guidance document. Obtaining this type of feedback should not be limited to public meetings or workshops; the Agency could meet with selected stakeholders and experts individually, and should do so when such meetings will advance the guidance development process. *See* 21 C.F.R. § 10.115(g)(1)(i) ("FDA can seek or accept early input from individuals or groups outside the Agency").

Further, to maximize the value and efficiency of the acceptance of stakeholder guidance, we recommend the Agency more clearly indicate those guidance document topics in which receipt of early draft versions will expedite the development process versus those areas in which the Agency is well down the path in developing a draft guidance document. To increase transparency, the Agency should provide feedback on information and drafts it receives from outside sources.

Recommendation: *The Task Force recommends that CDRH establish as a standard practice sending open "Notice to Industry" letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations on the basis of new scientific information. CDRH should adopt a uniform template and terminology for such letters, including clear and consistent language to indicate that the Center has changed its regulatory expectations, the general nature of the change, and the rationale for the change. Currently, manufacturers typically learn of such changes through individual engagement with the Agency, often not until after they have prepared a premarket submission. The aim of issuing a "Notice to Industry" letter would be to provide greater clarity to manufacturers, in a timelier manner, about the Center's evolving expectations with respect to a particular group of devices. Because a change in regulatory expectations would represent a change in policy, a "Notice to Industry" letter would likely be considered guidance, although it would typically be issued relatively quickly and would generally not contain the level of detail traditionally found in other guidance documents. In the interest of rapidly communicating the Center's current regulatory expectations to industry, 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. To expedite the issuance of "Notice to Industry" letters, CDRH should develop standardized templates for these letters and, as necessary, their accompanying Federal Register notices. In addition, when appropriate, CDRH should follow "Notice to Industry" letters as soon as possible with new or modified guidance explaining the Center's new regulatory expectations in greater detail and revising the guidance where necessary in response to comments received, so that external constituencies have a fuller understanding of the Center's current thinking. CDRH should also consider creating a webpage for identifying and explaining new information that has altered the Center's regulatory expectations, so that, across all CDRH-regulated products, external constituencies can better understand the rationale for changes in the Center's requirements.*

Although we support the Agency's recommendation to establish a standard practice for Notice to Industry (NTI) letters for use in conveying information for which the Center has changed its regulatory expectations on the basis of new information, we have several concerns and recommendations.

As part of the standard practice, we recommend the Agency clearly define 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 individually to companies with products already under review. Overuse of NTIs to communicate procedural topics, such as application format, or other topics that could be addressed via Level 2 guidance will reduce 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 standard practice should be recognition that whenever 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 real world situations it is important that the NTI standard practice include a mechanism for phasing in the new expectations, accepting alternate but equivalent measures and establishing implementation dates. Under 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 concern. This approach should continue to apply to NTIs, thus allowing a company to address the concern in another manner.

In addition to opening a docket, along with the issuance of an NTI, as recommended by the Task Force, we recommend that the Agency consider establishing a timeframe for reviewing comments submitted to the docket. Following issuance of the NTI, the Agency should work to incorporate the new information into draft guidance for review and comment within a specified period of time.

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. Importantly, the Agency should use additional tools to communicate to the industry in general, so that companies contemplating moving into the particular device market have visibility to 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 information 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.

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

Recommendation: *The Task Force recommends that CDRH take steps to improve medical device labeling, and to develop an online labeling repository to allow the public to easily access this information. The possibility of posting up-to-date labeling for 510(k) devices online is described in greater detail in the preliminary report of the 510(k) Working Group(described further in Section 3, below).*

AdvaMed does not support the development of an on-line labeling repository. AdvaMed has expressed concerns about the feasibility and value of this recommendation in a previous comment. Further, without an understanding of FDA's intent regarding the improvement of device labeling, we cannot support this proposal at this time.

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.*

Recommendation: *The Task Force recommends that CDRH 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. The SOP should include the expectation that when a decision is made to take a particular course of action, including a change in evidentiary expectations, the action and its basis should be communicated clearly and promptly to all affected parties. If it is not possible to provide complete detail about the basis for an action due to confidentiality concerns, Center staff should share as full an explanation as is allowable and state why a more complete explanation is not permissible. In addition, Center leadership should take steps to make sure that all employees have an accurate understanding of what information they are permitted to discuss with manufacturers, so that information that would help clarify the basis for a particular action is not needlessly withheld.*

AdvaMed suggests that all stakeholders be involved in developing the standard operating procedure. As with any process that involves and impacts multiple groups, acceptance of and conformance to the process improves when all stakeholders are involved. Importantly, the principles we outlined in our response to the "conceptual framework" proposal, should also be applied to any SOPs.

Recommendation: *The Task Force recommends that CDRH continue its ongoing efforts to make more meaningful and up-to-date information about its regulated products available and accessible to the public through the CDRH Transparency Website, consistent with the Center's FY 2010 Strategic Priorities and the work of the FDA Transparency Task Force. In addition to the pre- and postmarket information that is already available on CDRH Transparency Website, the Center should move to release summaries of premarket review decisions it does not currently make public (e.g., ODE 510(k) review summaries) and make public the results of post-approval and Section 522 studies that the Center may legally disclose. Making such information readily available to the public will provide CDRH's external constituencies with greater insight into the data that guide the Center's decisions and evolving thinking.*

As stated in our previous comments, AdvaMed supports the posting of reviewer summaries on a CDRH website, however, only those summaries for cleared devices should be released. Review summaries for devices that are not cleared would reveal company confidential information that would negatively impact marketing competitiveness and at the same time, serve no public health benefit because the product has not yet been made available to the public. An NSE determination is not the end of a company's product development. A company may resubmit the 510(k), pursue the *de novo* pathway, or submit a PMA. AdvaMed has submitted detailed comments on FDA's transparency initiative (see AdvaMed comments at Docket No. FDA-20098-N-0247) that articulate our strong concerns about FDA's proposed disclosure of confidential and proprietary information. For these reasons, AdvaMed supports making public only summaries of the results of post-approval and Section 522 studies that the Center may *legally* disclose.

ATTACHMENT A

Battelle
The Business of Innovation

510(k) Premarket Notification Evaluation

Prepared By:
Battelle Memorial Institute

For:
AdvaMed

September 2010

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510(k) Premarket Notification Evaluation

1. Introduction

This report analyzes Class I recalls of medical devices which were previously cleared through the United States Food and Drug Administration's (FDA's) 510(k) Premarket Notification Process. These recalls are compared to recalls of exempted devices as well as devices approved through the Premarket Approval (PMA) process. Data were gathered from publically available information from the FDA, as well as information made available by companies with affected products.

2. Executive Summary

FDA product recalls are actions taken when FDA-regulated products are defective or potentially harmful; Class I recalls are the most serious of these recalls, and represent products that may cause serious health problems or death. Data for Class I recalls of 510(k)-cleared devices in the United States were reviewed over a 64-month period, beginning January 1, 2005 and ending May 1, 2010 (hereafter referred to as the "review period"). There were, on average, 15 unique 510(k)-cleared device recalls per year between calendar years 2005 and 2009.

There have been 46,690 devices cleared through the 510(k) process since 1998—the year certain low-risk medical devices began to be exempted from premarket notification requirements (as part of The Food and Drug Administration Modernization Act (FDAMA)). This time period was selected because gathering data back to 1976 (the enactment of the 510(k) process) would include a large number of Class I devices which were later exempted from the 510(k) process by the FDAMA. This would inflate the total number of devices cleared, reducing the percentage of significant recalls for devices. The number of clearances/approvals from 1998 through May, 2010 was used to calculate recall percentages because it was assumed to be more representative of the number of products on the market potentially subject to recall rather than only using products cleared during the 64-month review period.

In this same time period since 1998, 2,825 devices have been approved through the Premarket Approval (PMA) process. This total includes PMA supplements representing significant changes: 180-day supplements and panel track supplements. 180-day supplements which are categorized as "no user fee" are excluded, as these filings are generally for minor changes such as manufacturing location or labeling which improves or clarifies warnings or precautions.

The table below details the number of devices with recalls over the review period of January 1, 2005, to May 1, 2010. Because the enactment date of FDAMA was used to calculate the total number of devices cleared or approved, recalled devices that were cleared or approved prior to the enactment of FDAMA were excluded from the total recall count and percentage calculations. Recalls of both 510(k)-cleared and PMA-approved devices represent a fraction of a percent of all total clearances or approvals, and a smaller percentage of recalls have been associated with 510(k) clearances than with PMAs (0.16% vs. 0.85%).

Number of Cleared or Approved Devices Recalled, Compared to all Clearances and Approvals Since 1998

Clearance or Approval Type	Total Number of Devices Cleared or Approved Since 1998	Class I Recalls: Jan. 2005 – May 2010	Percentage of Total
Devices - PMA	2,825[1]	24	**0.85%**
Devices - 510(k)	46,690	77	**0.16%**

Probable causes of device recalls were assessed based on available data from manufacturers and the FDA. Several assumptions were made in this assessment, and are detailed in Sections 3 and 5. According to this analysis, approximately 50% of the recall causes of 510(k)-cleared devices in the review period were attributed to design deficiencies (representing less than 0.1% of all 510(k) clearances since 1998), 29% to manufacturing deficiencies, and 6% to labeling deficiencies. The remaining 15% of 510(k)-cleared device recall causes were classified as "design or manufacturing," as data were not available to make a determination with a reasonable degree of confidence.

In the United States, medical devices are classified into three classes, Class I, II, and III, based on the level of control necessary to assure the safety and effectiveness of the device. Recalls of Class II devices represent 61% of all device recalls over the review period, followed by Class III devices at 28%. Class III devices, which primarily follow a PMA approval pathway, have recently (CY 2004-2008) represented approximately 15% of device approval and clearance totals at the FDA. This percentage includes both original PMA applications (1%) and supplements to PMA approvals (14%), with 510(k)s for Class I, II, and III devices constituting the remaining 85%.

In summary, devices cleared through the 510(k) Premarket Notification Process result in a smaller percentage of recalls (0.16%) than PMA approved devices (0.85%), and these recalls represent a fraction of a percent of all devices cleared or approved since enactment of the FDAMA.

More detailed results of the analysis, including charts and tables, are contained in Section 3. Assumptions made in the data analysis and data collection methods are detailed in Section 5.

[1] Includes 180-day supplements (excluding "no user fee" supplements) and panel track supplements.

3. Recalls of Devices Cleared through the 510(k) Premarket Notification Evaluation

Recalls are actions by a device manufacturer to correct a problem or remove a product from the market. Class I recalls are the most serious recalls, and involve a *"situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death*[2]*".* Recalls may be conducted on a manufacturer's own initiative, by FDA request, or by FDA order under statutory authority. Class I recalls can be issued for medical devices, drugs, biologics, and food. Only a portion of medical device recalls are for devices that have been cleared through the 510(k) Premarket Notification Process.

Recall data for 510(k)-cleared devices were evaluated over an approximate five year review period, from January 1, 2005 to May 1, 2010. Recalls of PMA-approved devices are referenced for comparative purposes.

3.1. Number of Unique Recalls

United States Class I medical device recalls were gathered from the FDA's "Medical Device Recalls" database[3] on May 6, 2010, resulting in several hundred line-item recalls. Some line item recalls were then grouped with similar entries. This grouping methodology is outlined below:

- Recalls were grouped when different model numbers of the same product were recalled, provided the products were likely marketed under the same 510(k) or PMA and involved the same root cause.
- Recalls were grouped when products were re-branded for sale under different trade names, provided the products were likely marketed under the same 510(k) or PMA and involved the same root cause.
- Recalls were grouped when a recall was expanded to additional manufacturing lots of the same product for the same root cause.
- Recalls were grouped when a recall involved a single manufacturer for systemic production or quality issues over a limited time period. For example, a failure to follow Good Manufacturing Practices[4] (GMP) across several product lines.

The FDA's weekly "Enforcement Reports"[5] and the FDA's "List of Device Recalls"[6] were used to aid in this grouping process.

Device recalls were then categorized based on the devices' likely clearance or approval histories, using data available in the FDA's PMA and 510(k) databases.

Figure 1 compares the total number of Class I recalls for 510(k)-cleared devices with other device recalls over the review period of January 1, 2005, to May 1, 2010. "Other Devices" includes devices exempt from Premarket Notification or Approval, or devices marketed without receiving an appropriate clearance, approval, or exemption.

[2] United States Code of Federal Regulations, 21 CFR 7.41.
[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm
[4] United States Code of Federal Regulations, 21 CFR 110.
[5] http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm
[6] http://www.fda.gov/medicaldevices/safety/recallscorrectionsremovals/listofrecalls/default.htm

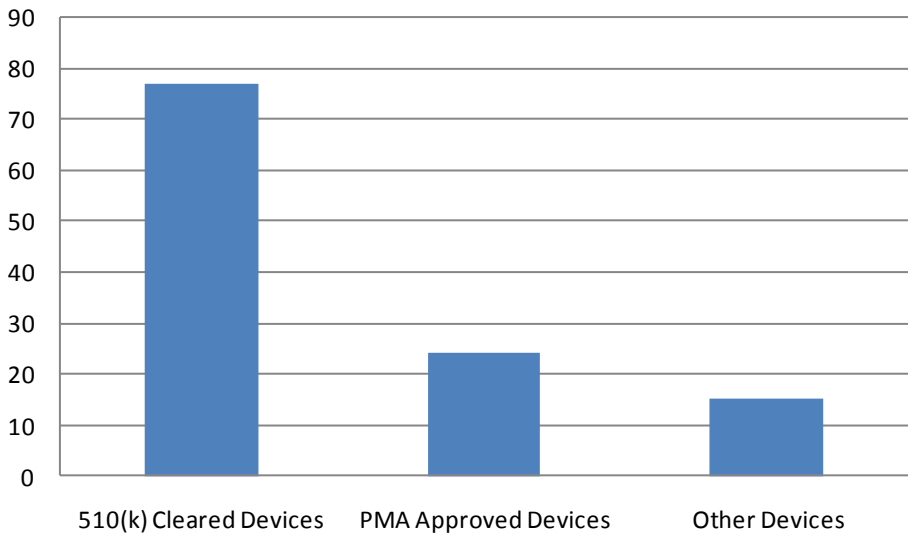

Figure 1: Number of Device Recalls.

3.2. Number of Class I Recalls Compared to the Total Number of Products Cleared or Approved

The total numbers of device clearances and approvals since 1998 were used as relative indications of the respective number of devices on the market. In 1997, the U.S. enacted the Food and Drug Administration Modernization Act (FDAMA), which represents the last major change to the FDA's clearance and approval regulations, and included a 510(k) filing exemption for certain low risk medical devices (e.g. tongue depressors). This premarket notification exemption was implemented in early 1998[7]. Table 1 below displays the percentage of devices recalled during the review period as compared to the total number cleared or approved since 1998. Devices with 510(k) clearances represent the smallest percentage of Class I recalls when compared to the total number of clearances or approvals. The PMA totals include both PMAs and PMA supplements representing significant changes: 180-day PMA supplements (excluding "no user fee" supplements) and panel track supplements.

Table 1: Number of Cleared or Approved Devices Recalled, Compared to all Clearances and Approvals Since 1998.

Clearance or Approval Type	Total Number of Devices Cleared or Approved Since 1998	Class I Recalls: Jan. 2005 – May 2010	Percentage of Total
Devices – PMA	2,825[8]	24	**0.85%**
Devices - 510(k)	46,690	77	**0.16%**

[7] On February 2, 1998, the FDA published a notice in the Federal Register announcing a list of Class I devices that it considered to be exempt from premarket notification effective February 19, 1998.
[8] Includes 180-day supplements (excluding "no user fee" supplements) and panel track supplements.

3.3. Device Recall Causes

This section presents the most likely causes of Class I recalls for 510(k)-cleared and PMA-approved devices, based on available data.

The determination of cause for some recalls was straightforward, such as a "manufacturing" cause for a device manufactured without following Good Manufacturing Practices (GMP). Other cause determinations had to be inferred through often limited information available in the recall text, press releases, and the manufacturers' published data. The "Assumptions" section, Section 5.1, details these uncertainties in greater detail.

The cause categories used for the device analysis are detailed below:

Manufacturing
These recalls include causes that were most likely related to manufacturing deficiencies. These causes may include failure to maintain sterility, failure to follow GMP, or manufacturing QC deficiencies.

Design
These recalls include causes that are likely due to flaws inherent in the design of the device, either created initially or through approved design changes (e.g., part obsolescence).

Manufacturing or Design
Recalls in this category could either be due to manufacturing or design causes. The information available for these recalls does not indicate the cause of the recall, other than the root cause was likely either in design or manufacturing. This category was employed due to frequent lack of comprehensive information provided by the FDA's recall notice and the device manufacturers. An example may include a failed electronic component, where no data are given as to why it failed; the component failure may be tied to the initial design not accounting for tolerances, or a supplier quality issue delivering out-of-specification components.

Labeling
These recalls result from a labeling deficiency (though these issues may ultimately result from a manufacturing or a design root cause).

Table 2 presents the likely cause of Class I recalls for 510(k)-cleared and PMA-approved devices, using the categories mentioned above. These causes are presented as a percentage of total devices marketed since 1998. As previously mentioned, total PMA devices include panel track supplements and 180-day supplements, excluding "no user fee" supplements. The analyses include recalls issued between January 1, 2005, and May 1, 2010.

Table 2: Percentage of Device Recall Causes, Compared to Total Number of Devices Cleared or Approved Since 1998.

Clearance or Approval Type	Recalls as a Percentage of Total Devices Since 1998	Recalls due to Design Causes	Recalls due to Manufacturing Causes	Recalls due to Labeling Causes	Recalls due to Manufacturing or Design Causes
Devices - PMA	**0.85%**	**0.46%**	**0.18%**	**0.11%**	**0.11%**
Devices - 510(k)	**0.16%**	**0.08%**	**0.05%**	**0.01%**	**0.03%**

3.4. Device Recall Requirements

A variety of impacts to devices currently on the market can occur when a Class I recall is initiated. Four categories were used in this research:

Removal from Inventory:
The device under recall was required to be removed from operation. The methods included destroying devices, returning devices to the manufacturer, or on-site removal by the manufacturer. Often, refurbished or replacement devices were provided to the customers.

Field Fix:
The device under recall could be repaired in the field, either by the manufacturer or the user. These fixes often included software upgrades or replacement components.

Labeling:
These recalls addressed a product deficiency which could be mitigated with a labeling change. Recalls initiating a labeling change may provide labeling updates electronically, through mail, or through an on-site call by the manufacturer.

Monitor for Conditions:
The requirements for these recalls included the monitoring of patients or equipment for adverse events. This included monitoring patients with potentially defective implantable devices.

Figure 2 outlines the field requirements of Class I 510(k) device recalls and Figure 3 outlines the field requirements of Class I PMA device recalls, using the categories outlined above. The review period was January 1, 2005, to May 1, 2010.

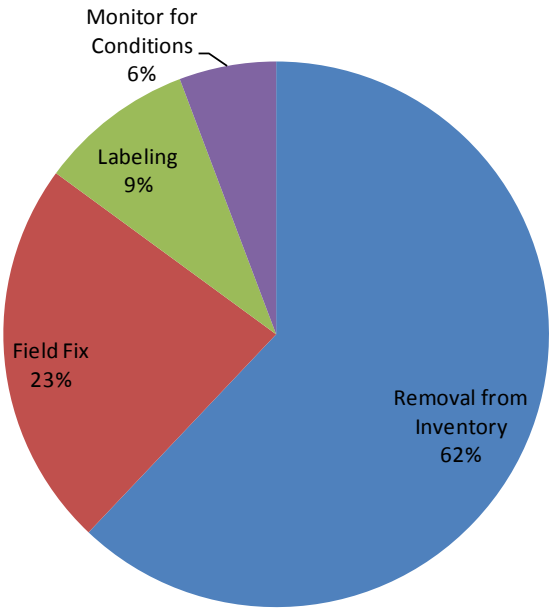

Figure 2: Field Requirements for Class I 510(k) Device Recalls.

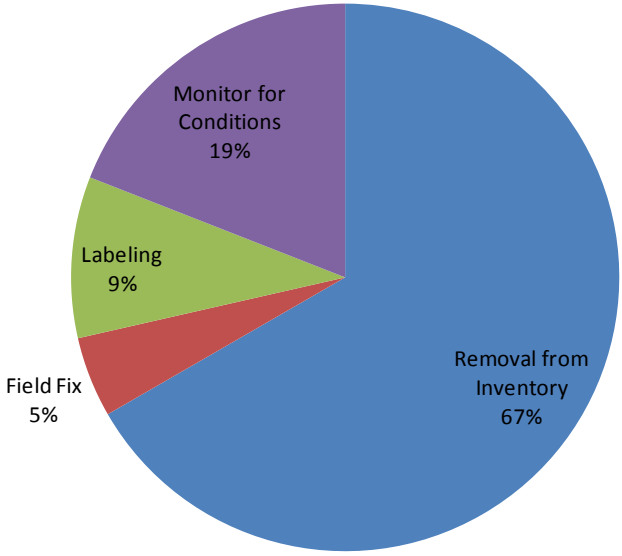

Figure 3: Field Requirements for Class I PMA Device Recalls.

3.5. Clearance and Approval History of Recalled Devices

Clearance or Approval Type

Devices that have undergone a Class I recall meet one of the following four conditions:

- The device has been cleared through the 510(k) process (Special, Traditional, or Abbreviated 510(k)).
- The device has been approved through a Premarket Approval Application (PMA).
- The device has been exempted from clearance or approval because the device is one that was in commercial distribution before May 28, 1976, the enactment date of the Medical Device Amendments.
- The device was not cleared, approved, or exempted through any of the three pathways above.

The 510(k) or PMAs associated with the recall could not always be identified with a high degree of confidence, as manufacturers and model numbers may change without notification to the FDA. In addition, manufacturers may have renamed the product or produced derivative products that did not require a separate filing. The "Assumptions" section, Section 5.1, details the methodology and assumptions used to determine the most likely 510(k) or PMA associated with the recall. Figure 4 indicates the clearance / approval history of the Class I recalled devices over the review period.

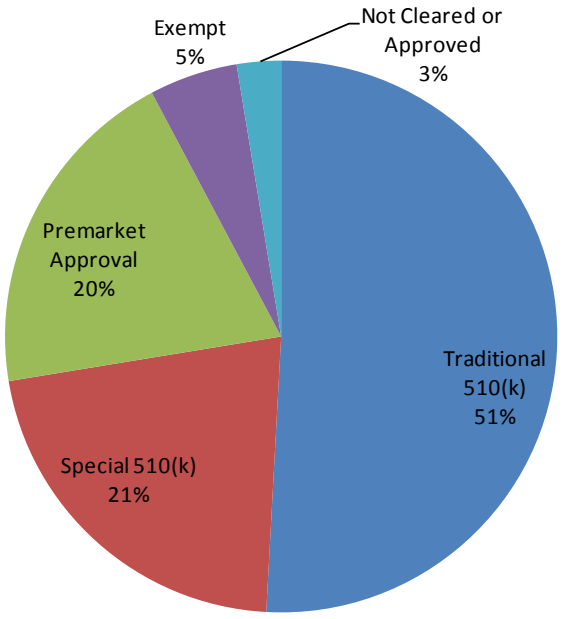

Figure 4: Clearance/Approval Routes of Class I Device Recalls.

3.6. Device Class and Type Recalled

This section documents Class I recalls by device classification, according to the FDA's classification system. The FDA has established classifications for roughly 1,700 medical devices and grouped them into 16 device panels. Each of these generic types of devices is assigned to one of three regulatory classes (I, II, or III), based on the level of control necessary to assure the safety and effectiveness of the device. Data are based off the 510(k) or PMA associated with the recalls.

Device Classification

The three U.S. medical device classes and the requirements which apply to them are:

- Class I: (General Controls)
  - With Exemptions
  - Without Exemptions
- Class II: (General Controls and Special Controls)
  - With Exemptions
  - Without Exemptions
- Class III: (General Controls and Premarket Approval)

The class to which a device is assigned determines, among other things, the type of premarketing submission/application required for FDA clearance to market. If the device is classified as Class I or II, and if it is not exempt, a 510(k) is required for marketing. All devices classified as exempt are subject to the limitations on exemptions[9]. For Class III devices, a premarket approval application (PMA) is required unless the device is on the market prior to the passage of the medical device amendments in 1976, or substantially equivalent to such a device (and PMA's have not been called for).

Figure 5 displays the device classification of Class I recalled devices over the review period. Figure 6 shows the percentage of devices cleared or approved over a 5 year period from 2004 through 2008[10] for comparative purposes; however, no data are available to indicate the number of preamendment or 510(k) exempt products placed on the market in this timeframe.

[9] Limitations of device exemptions are covered under 21 CFR xxx.9, where xxx refers to Parts 862-892.
[10] FDA ODE, Annual Performance Report, FY 2008.

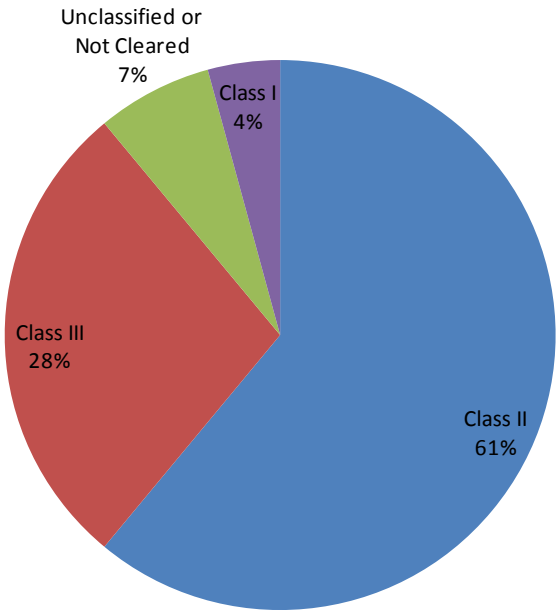

Figure 5: Device Classification of Class I Recalls.

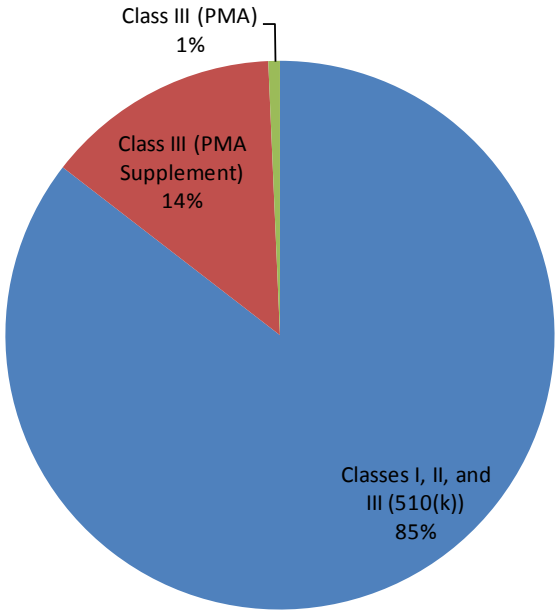

Figure 6: Device Classification of All Clearances and Approvals, FY 2004-2008 (FDA).

4. Conclusion

The number of devices with post-FDAMA 510(k) clearances that have undergone a Class I recall between January 1, 2005 and May 1, 2010—approximately 77—represents less than 0.16% of the 46,690 devices that have been cleared through the 510(k) Premarket Notification Process since 1998. This represents a significantly smaller percentage than Class I recalls of PMA approved devices at 0.85%.

5. Appendices

5.1. Assumptions

The following list outlines key assumptions made while collecting and analyzing the data presented in this report.

1. Data were based on publicly available information on the FDA's website, www.fda.gov, and a limited number of press releases and news external to the FDA's website. Data were collected from May 6, 2010 to May 26, 2010. Data from these sources were assumed to be accurate and complete.

2. Recall data—including letters to medical professionals, press releases, enforcement reports, and supplementary information—did not include data on the devices' clearance or approval histories. Therefore, the authors had to surmise the most likely 510(k) or PMA associated with each recall. In many cases, trade names and manufacturers listed in the device recalls are not the same as those listed in the devices' 510(k)s and PMAs, due in part to mergers, acquisitions, or re-branding.

3. In a majority of cases, recall data—including letters to medical professionals, press releases, enforcement reports, and supplementary information—did not provide adequate data to determine with certainty the root cause of the device recalls. In particular, determining cause between "design" and "manufacturing" was particularly uncertain; in many cases the authors had to surmise the most likely cause of the recall, or bin the data into a combined group—"Design or Manufacturing". Certain rules were used to assign recalls to particular categories. These include:

    - Failure to maintain or assure sterility: manufacturing.
    - Failure to follow GMP: manufacturing.
    - All labeling issues: labeling (whether root cause was design or manufacturing).
    - Software "bug" (except where due to failure in software manufacturing processes): design.
    - Recall of specific lots of an established product: manufacturing.

4. Similar line item recalls across a limited date range were considered to be a single recall. For example, cases where a recall was expanded to additional lots or product lines were considered to be a single recall.

5. Approximately 5% of device recalls which were not associated with preamendment or exempt devices could not be associated with a 510(k) or PMA with a reasonable degree of certainty. These recalls were not included in the tally of device class, but were included in the count of number of medical device recalls per year.

6. Because the enactment date of FDAMA was used to calculate the total number of devices cleared or approved, recalled devices that were cleared or approved prior to the enactment of FDAMA were excluded from the total recall count and percentage calculations.

5.2. Data Sources and Collection Methods

On May 6, 2010, an initial list of Class I device recalls was queried from the database located at:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm

The following search parameters were selected:

- Product name: blank
- Recall class: 1
- Recall number: blank
- Reason for recall: blank
- Recalling firm: blank
- Sort by: Date Record Posted (Descending).

From this list, recalls were combined into logical groupings, based on recall text and other available data, including the "Recall Summary" page, located at:

http://www.fda.gov/medicaldevices/safety/recallscorrectionsremovals/listofrecalls/default.htm

Once recalls were recorded and grouped, 510(k)s and PMAs associated with the recalls were researched.

For 510(k)s, the primary method of research included searching the FDA website for 510(k) summary information through an external search engine (Google). The following example search demonstrates the format that was used:

```
site:fda.gov filetype:pdf 510(k) Guidant pacemaker
```

For PMAs, the FDA's PMA database was used for research, as well as search engine queries:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

After an initial list of potential 510(k)s and PMAs were determined, the search was narrowed and modified to key-in on specific model names or features that were present in the recalled

devices. Company websites, literature, and published information were used to gain confidence that the appropriate 510(k) or PMA was selected.

Once the 510(k) or PMA had been selected, information was recorded from the submission and clearance/approval, including device classification and panel, clearance/approval date, and clearance/approval route.

ATTACHMENT B

AdvaMed
Advanced Medical Technology Association

AdvaMed Legal Analysis of Rescission Authority

In its proposal, the 510(k) Working Group recommends:

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

510(k) Working Group Preliminary Report and Recommendations at 58. Under current law, FDA does not have statutory authority to rescind a 510(k) substantial equivalence determination, and this authority cannot be implied from policy or other non-statutory grounds. Consequently, without a basis in the Federal Food, Drug, and Cosmetic Act (FD&C Act), the agency cannot promulgate regulations defining rescission authority. FDA can only nullify a finding of substantial equivalence if the 510(k) applicant committed fraud in seeking that determination or, in very limited circumstances, based on inadvertent administrative mistakes or errors by the agency.

Rescinding a 510(k) would not only reclassify a device, but would reclassify all devices that relied upon the device subject to rescission, and would do so without adhering to the reclassification requirements in the FD&C Act for new devices, *see* § 513(e). Effectively, the Working Group and the Center for Devices and Radiological Health (CDRH) are using so-called rescission as an enforcement tool for removing undesirable devices from the market, instead of removing such devices through the exercise of the agency's substantial and broad enforcement authority. If the agency believes it is important to remove a device from use and eliminate it as a predicate, under the law what FDA must do is obtain a judicial order finding a device is misbranded or adulterated, thus, eliminating the device as a predicate in the premarket notification process, *see* § 513(i)(2). Alternatively, FDA could reclassify the device into class III, assuming the administrative record would support reclassification. Rescission is unnecessary to protect the public health, and as we discuss below, neither the agency's bases for rescission proposed in 2001, nor its current statements support or create rescission authority.

I. FDA DOES NOT HAVE STATUTORY AUTHORITY TO RESCIND 510(K)s BASED ON SUBSTANTIVE OR POLICY GROUNDS AND CANNOT PROMULGATE REGULATIONS DEFINING THAT AUTHORITY.

A. FDA does not have authority under the FD&C Act to rescind 510(k)s.

The FD&C Act does not directly or indirectly authorize FDA to rescind substantial equivalence orders. Under that Act, Congress explicitly gave FDA the authority to

withdraw premarket approvals (PMAs) (§ 515(e)(1)), investigational device exemptions (IDEs) (§ 520(g)(5)), and product development protocols (PDPs) (§ 515(f)(7)). The authority to classify devices under sections 510(k) and 513(f)(1) (and later 513(i)) did not include the authority to rescind classifications. Consistent with the rule of statutory construction, if the legislature did not include withdrawal or rescission authority, it was not intended. The FD&C Act's remedy for an incorrect classification was and is reclassification. Indeed, Congress identified separate reclassification provisions for each group of devices that were subject to classification under the Act: preamendment devices and those substantially equivalent to them (§ 513(e)); postamendment class III devices (§ 513(f)(3)); and transitional devices (§ 520(l)(2)). No analog to withdrawal authority exists for premarket notification orders because these orders are not approvals, *see* 21 CFR § 807.97 (deeming 510(k) devices misbranded when represented as receiving FDA approval), like the administrative orders that are subject to withdrawal.

Even the fact of an approval did not by itself imply the authority to withdraw an approval. In the drug context, Congress recognized that the power to approve does not imply the power to withdraw. Specifically, in 1938, it gave FDA the power to approve new drug applications (NDAs); in 1962, it gave FDA the power to withdraw such applications. The 1962 provision would have been unnecessary if the power to approve NDAs had included or implied the power to withdraw them. If an approval did not entail the power to withdraw the approval, certainly FDA cannot through a miracle of words create withdrawal or rescission authority for a classification, particularly when the statute explicitly provides for reclassification authority.

Because premarket notification under the FD&C Act is a means of classifying devices, rescinding a 510(k) clearance would reclassify that device. Reclassification of preamendment devices, including substantially equivalent devices, is governed by section 513(e) of the FD&C Act. That provision permits reclassification through rulemaking if FDA has "new information" to justify the result. Under section 513(e), FDA may reclassify a type of class III device into class II or class I, or may reclassify a type of class II device into class I. *See* 21 C.F.R. § 860.130(c). Rescinding a 510(k) would reclassify substantially equivalent class I and II devices into class III. Consequently, if FDA asserts the authority to rescind a device's marketing clearance for any reason, at any time, the agency would be substituting its judgment for that of Congress, and would change a device's classification in a way not anticipated or permitted under the FD&C Act. Rescission of a 510(k) device classification would be an agency-created reclassification remedy without basis in the FD&C Act.

FDA cannot promulgate regulations that exceed the authority granted to it under the FD&C Act. Section 701(a) of that Act grants FDA "the authority to promulgate regulations for the efficient enforcement of [the FD&C Act]." However, section 701(a) does not give FDA unlimited regulatory powers; "regulations issued under that section must effectuate a Congressional objective expressed elsewhere in the Act." *Pharm. Mfrs. Ass'n v. FDA*, 484 F.Supp. 1179, 1183 (D.Del. 1980), *aff'd* 634 F.2d 106 (3d Cir. 1980).

In *U.S. v. Nova Scotia Food Products*, 568 F.2d 240 (2d Cir. 1977), the U.S. Court of Appeals for the Second Circuit stated that section 701(a) of the FD&C Act is "analogous to the provision 'make . . . such rules and regulations as may be necessary to carry out the provisions of this Act,' in which case the 'validity of a regulation promulgated thereunder will be sustained so long as it is 'reasonably related to the purposes of the enabling legislation.'" *Nova Scotia Food Prods.*, 568 F.2d at 246 (citations omitted). The U.S. District Court for the District of Columbia pointed out that section 701 of the FD&C Act "does not constitute an independent grant of authority that permits FDA to issue any regulation the agency determines would advance the public health. Rather, § [701] permits the FDA to use rules as a means of administering authorities otherwise delegated to it by the Congress." *Ass'n of Am. Physicians and Surgeons v. FDA*, 226 F.Supp.2d 204, 213 (D.D.C. 2002). Because the FD&C Act does not grant FDA the authority to rescind 510(k)s, none of the agency's regulations can express or imply such authority.

In 2001, FDA asserted in a proposed rule that its administrative procedure regulations (specifically, 21 C.F.R. §§ 10.33(a), (h), and 10.75) provide the authority to rescind 510(k)s. *See* 66 Fed. Reg. 3523, 3524 (Jan. 16, 2001). It is improper for the agency to rely on a regulation as authority to issue another regulation. Indeed, FDA's regulations cannot provide it with authority that was not conferred by Congress in the first place. Without authority from the FD&C Act, FDA cannot issue additional regulations to rescind 510(k) device classifications.

B. FDA does not have implied power to rescind 510(k)s.

Understanding there was no statutory basis for rescission, FDA in the past asserted its recession authority derived from federal case law that recognizes an implied authority for agencies to reconsider administrative actions, even if the applicable statutes and regulations do not provide for reconsideration. *See* 66 Fed. Reg. at 3524. However, that case law provides a narrow implied authority for tribunals to reconsider actions before the time for an appeal of the action has lapsed; it does not imply the authority to revoke a vested interest, such as a 510(k) classification determination. The cases make clear that the implied authority to reconsider a matter only exists until jurisdiction lapses, *i.e.*, a decision becomes final.

For example, in *West v. Standard Oil Company*, 278 U.S. 200 (1929), the U.S. Supreme Court ruled that the Secretary of Agriculture had authority to consider a dispute about the character of contested lands, notwithstanding that the Secretary had previously ordered a dispute over the lands dismissed. The Court's holding that the order of dismissal was not a final act hinged on two factors. First, the Court found that the dismissal did not reflect a determination on the merits following a full evaluation of the facts. *See id.* at 213. Second, and more importantly, the Court determined that the dismissal did not result in a patent, or an instrument embodying a binding determination of rights in the land. *See id.* at 219 (after issuance of an order conferring rights, administrative findings of fact relied upon in issuing the order "are conclusive, in the absence of fraud or mistake"). For these

reasons, the Court found that no final order had issued, and jurisdiction remained with the Secretary. After jurisdiction lapses, however, there is no implied agency authority to reconsider and alter a previous order. *See Prieto v. United States*, 655 F. Supp. 1187 (D.D.C. 1987) (rejecting the Department of the Interior's revocation of the trust status of certain lands because the Department had failed to issue its reconsideration within the thirty day period permitted for appeals, and its jurisdiction over the trust status of the lands therefore ceased).

Timing is critical to an agency's ability to reconsider its actions. In *Albertson v. FCC*, a case frequently cited for the principle that "the power to reconsider is inherent in the power to decide," the reconsideration fell within the 20-day period permitted for an appeal of the administrative board's initial decision. *See* 182 F.2d 397, 399 (D.C. Cir. 1950). The *Albertson* court wrote: "the power of the Commission to hear and determine matters arising under the rehearing provision . . . carries with it by implication the authority to reconsider . . . within the twenty days allowed for an appeal. . . . That is so, for within such period jurisdiction over the contested order remains with the commission." *Id.* Thus, while this decision has occasionally been cited for a broad power of an agency to reconsider its actions, *see Civil Aeronautics Bd. v. Delta Airlines, Inc.*, 367 U.S. 316, 339 (1961) (dissenting opinion), the case in fact is a restatement of the principle of *Standard Oil* that an agency may reconsider its actions, but only before passage of time or other events render the action final.

Once FDA issues its substantial equivalence order, a device's classification and marketing status are final. On the day a substantial equivalence decision is received, the product could be marketed and the review process would lapse. At this stage, the case law FDA relies upon would bar a change in the device's classification status, except through a Congressionally-mandated statutory process. At best, FDA could argue that under § 517(a)(8) of the FD&C Act it has 30 days until jurisdiction would lapse to reconsider a classification decision under section 510(k)/513(f)(1) because any interested party could appeal a substantial equivalence determination. Even if one accepted this view, FDA's authority to reconsider a premarket notification classification decision would lapse after 30 days, coincidental with the expiration of the time period for an appeal.

In sum, FDA simply cannot rely on the principle of an implied power of reconsideration to authorize rescission at any time after the agency issues an order of substantial equivalence. Such a rule would be unlawful because it would effectively deny finality to any FDA order, and would be at odds with judicial authority that unequivocally states that an agency's jurisdiction to reconsider a matter ceases when an order becomes final. Although FDA could argue that a substantial equivalence order remains open until all appeal rights are extinguished, even then the agency would have only 30 days to reconsider a premarket notification classification order.

II. FDA CAN ONLY NULLIFY A FINDING OF SUBSTANTIAL EQUIVALENCE IN CASES OF FRAUD OR ADMINISTRATIVE MISTAKE OR ERROR.

As the 510(k) Working Group points out in its CDRH Preliminary Internal Evaluations Report, "agencies have inherent authority to reconsider their decisions in certain circumstances, such as where there has been fraud or error, and to rectify their mistakes." 510(k) Working Group Preliminary Report and Recommendation at 58. However, this authority does not create a basis for 510(k) rescission authority. Rather, it allows the agency to nullify substantial equivalence determinations in the rare case of fraud or administrative mistake or error.

For example, in *American Trucking Association v. Frisco Transportation Company*, 358 U.S. 133 (1958), the U.S. Supreme Court rested its ruling that an administrative agency may correct inadvertent errors in its decision-making upon a factual finding that the Interstate Commerce Commission's failure to specifically reserve authority in trucking certificates to cancel the certificates was clerical inadvertence or mistake rather than a policy change. 358 U.S. at 146. This principle would permit FDA to reconsider, without express statutory authority, any decision reflecting clerical errors, for example, were a reviewer to inadvertently omit the letter "N" before "SE." The principle does not, however, permit the agency to rescind a substantial equivalence determination on substantive grounds, for example, an agency reassessment of data or receipt of new safety and effectiveness information that put in question a prior determination. *See Concerned Citizens of Bridesburg v. EPA*, 836 F.2d 777, 786 (3d Cir. 1987) (distinguishing typographical errors from substantive agency determinations resulting in approvals).

The 510(k) Working Group cites *American Therapeutics Institute v. Sullivan*, 755 F. Supp. 1 (D.D.C. 1990), as authority that agencies can reconsider decisions in certain circumstances. The decision in *American Therapeutics Institute* is consistent with the line of cases construing a narrow administrative authority to reopen orders that may be legitimately characterized as mistakes. Specifically, the court dismissed a pharmaceutical company's case against FDA challenging the agency's summary rescission of an NDA six weeks after its issuance on grounds of inadvertence because FDA rescinded on the basis of information that existed at the time of the approval and that, if known by the reviewing official during the application's review, would have resulted in disapproval. However, the court's holding only reflects the determination that the agency's use of rescission shortly following an inadvertent error was not so clearly ultra vires as to justify its intervention in a matter properly resolved by the court of appeals, which had exclusive jurisdiction to hear appeals of NDA denials under section 505(h) of the FD&C Act. *See id.* at 2. Far from establishing a precedent permitting 510(k) rescission, the case is extremely limited and only demonstrates the reluctance of a district court to intervene in a statutorily-defined appeals scheme after determining that the case presented "an unresolved issue of statutory interpretation and administrative law within the exclusive jurisdiction of the Court of Appeals." *Id.* The district court determined it was without

jurisdiction to grant relief against the government, unless FDA's action was clearly beyond the scope of its authority, and that the court of appeals had exclusive jurisdiction to determine whether the agency's denial of an NDA was lawful.

Importantly, courts have taken strong exception to attempts by agencies to change past actions through purported corrections of mistakes based upon inadvertence or fraud as a means to legitimize changes in policy. For example, in *Prieto v. United States*, 655 F. Supp. 1187 (D.D.C. 1987), the court wrote that "perhaps the most compelling reason" of several for rejecting the attempted revocation of a trust status was the Department of Interior's pretext in relying on an unfounded assertion of fraud to "bootstrap de novo review" of its initial determination. *Prieto*, 655 F. Supp. at 1192. In another illustrative case, after reviewing a record that clearly demonstrated a policy change, the court in *Concerned Citizens of Bridesburg v. EPA*, 836 F.2d 777 (3d Cir. 1987), rejected EPA's efforts to characterize approvals of state odor provisions as "inadvertent" where the agency had relied on the approvals in several other decisions in a thirteen year period, concluding the agency's efforts to revise its approvals reflected "a clear change in policy." *Concerned Citizens of Bridesburg*, 836 F.2d at 786.

The case law provides agencies with narrow authority to reconsider and reverse previous decisions in the case of fraud or administrative mistake or error. In the 510(k) context, FDA would be allowed to nullify substantial equivalence determinations if fraud was used to obtain a substantial equivalence order, or the substantial equivalence determination reflected clerical or other administrative errors. The case law relied upon by the Working Group does not, however, permit the agency to nullify a 510(k) determination on substantive grounds.

III. RESCINDING ONE 510(K) CLEARANCE COULD RECLASSIFY AN ENTIRE GROUP OF DEVICES.

The 510(k) clearance process is a classification system based on predicate devices' classifications. Consequently, rescission of one 510(k) clearance would reclassify not only that device, but all devices that FDA determined to be substantially equivalent to it. This result would adversely affect all individuals whose rights to market such devices derive from a rescinded 510(k). In fact, the effect of a rescission on a predicate device, and all devices classified through reliance on the rescinded predicate, would be a reclassification into class III independent of the FD&C Act's reclassification authority, and a resulting PMA requirement before marketing. Permitting rescission would result in the denial of a statutory process that is intended not only to protect individual interests, but the public health.

Rescission of a 510(k) is unlike the withdrawal of a PMA, IDE, or PDP. These withdrawals are specifically authorized under the FD&C Act, and are product specific. Withdrawal of a PMA, IDE, or PDP only has direct regulatory consequences for a single product, and prior to a withdrawal becoming final, the FD&C Act prescribes protections

for the potentially affected party. In contrast, rescission of a predicate exceeds the interest of an individual and has potentially far reaching consequences, yet is unauthorized by the FD&C Act, and therefore, without protective processes to avoid governmental error or abuse.

Several concerns flow from the principle that rescission of a 510(k) is a reclassification action. First, as described below, assuming, arguendo, the existence of rescission authority, each potentially adversely affected person must be provided with adequate notice and an opportunity to participate in the rescission process. It is not enough for FDA to engage the 510(k) holder. Second, several express reclassification authorities exist under the FD&C Act. An effort by the agency to add a new one without a statutory basis warrants close scrutiny to ensure that FDA has not deviated from the legislative intent regarding device classification. Last, close scrutiny is warranted to ensure that the agency is not trying to circumvent use of its enforcement authority through the creation of an administrative substitute without adequate procedural protections.

IV. ASSUMING AUTHORITY TO RESCIND 510(K) CLASSIFICATION DETERMINATIONS, ANY RESCISSION REGULATION WOULD BE ACCOMPANIED BY AND INCLUDE SUBSTANTIAL PROCEDURAL PROTECTIONS AND RESOURCE BURDENS FOR FDA.

The 510(k) Working Group recommends that CDRH consider the procedures that would be necessary to rescind a 510(k). As stated above, the rescission of one 510(k) clearance would adversely affect all individuals whose right to market a device is derived from the rescinded 510(k). Any agency action with binding consequences for a group of individuals requires notice to all members of the group with an opportunity for comment. This is a basic principle of administrative law, *see* 5 U.S.C. § 553, and inherent in the FD&C Act's reclassification provision for preamendment devices and devices substantially equivalent to them, *see* § 513(e) (requiring notice and comment rulemaking to reclassify devices to a lower classification).

If one assumes that FDA has the authority to rescind a 510(k), notice of the basis for the agency's rescission cannot be limited to the 510(k) holder of record. FDA's regulations require the agency to announce administrative action "of general or particular applicability and future effect" in the Federal Register. 21 C.F.R. §§ 10.3(a), 10.40(b). Further, to satisfy the Administrative Procedure Act and 21 C.F.R. Part 10, the notice must provide an adequate description of the bases for the agency action to allow meaningful comment by affected parties. 5 U.S.C. § 553(b); 21 C.F.R. § 10.40(b)(1)(vii). Thus, legally sufficient notice and the opportunity to comment must be provided to all individuals whose marketing clearance may be invalidated by a rescission.

In addition to notice and comment rulemaking, FDA must provide adequate procedural protections for each member of the class affected by the rescission. Because a substantial equivalence order permits marketing of a device based on the device's classification,

issuance of the order effectively creates a property right that FDA has recognized in the context of persons selling their substantial equivalence orders and access to the agency file that supported the device's classification and clearance determination. *See* FDA, CDRH, *Device Advice, Device Regulation and Guidance: Medical Devices – Premarket Notification 510(k), at* http://www.fda.gov/MedicalDevices/DeviceRegulationand Guidance/GuidanceDocuments/ucm150086.htm (stating that "a 510(k) may be bought, sold, or transferred. FDA is not involved in transfers of ownership. The new owner should maintain information documenting the transfer of ownership of a 510(k), including any legal transactions that took place, in its 510(k) files.").

Before the agency may abrogate such rights, it must provide each potentially adversely affected party with adequate process for challenging the factual basis of a revocation, as applied to that party. *See e.g.*, *Londoner v. Denver*, 210 U.S. 373 (1908) (requiring hearings for actions affecting identifiable individuals "who were exceptionally affected, in each case upon individual grounds").

The FD&C Act is consistent in defining the procedural rights of persons facing the loss of marketing rights, e.g., device and drug approvals. Specifically, when the agency undertakes to withdraw a device's PMA, the Act requires that the agency issue notice to the affected party and an opportunity for an informal hearing to challenge the proposed withdrawal order. Thereafter, if the PMA is withdrawn, the FD&C Act provides the affected person the option of an independent advisory committee review or a formal evidentiary hearing before an administrative law judge to challenge the agency's order to withdraw a PMA. In light of the strong protections afforded in other instances of agency revocation of marketing rights, the proposal's provision of only the right to an opportunity for an informal hearing is inadequate, and arbitrary and capricious. *See, e.g.*, *Teva Pharm. USA Inc. v. FDA*, 182 F.3d 1003 (D.C. Cir. 1999) (inconsistent treatment by the agency of similar situations is arbitrary and capricious).

Important protections afforded under Part 12 of FDA's regulations include a full evidentiary hearing, the right to cross-examine witnesses, an administrative law judge, and a greater opportunity to discover the agency's case than that provided in an informal hearing. These protections are critical to the accurate resolution of factual disputes such as those that would arise in the context of a proposed 510(k) rescission. All parties whose interests would be harmed because of factual and legal conclusions reached by the agency regarding a marketed class I or II device, *i.e.*, a predicate device, must have effective opportunities to contest the facts that underlie the proposed rescission.

Further, any regulation proposed by FDA regarding 510(k) rescission would be a "significant" regulatory action under an Executive Order governing regulatory planning and review, and would require review by the Office of Management and Budget's (OMB's) Office of Information and Regulatory Affairs (OIRA). Under Executive Order number 12866, as revised by Executive Order number 13258 and Executive Order number 13422, "[f]ederal agencies should promulgate only such regulations as are

required by law, are necessary to interpret law, or are made necessary by compelling public need." Exec. Order No. 12866, 58 Fed. Reg. 51,735, 51,735 (Oct. 4, 1993). This Executive Order requires agencies to annually provide OMB with a regulatory plan that includes a list of significant planned regulatory actions and the legal bases for such actions (e.g., "whether any aspect of the action is required by statute or court order") for review by OIRA. *Id.* at 51,738. OIRA circulates each agency's regulatory plan to regulatory policy advisors, for example, the OMB Director, and other agency heads. *Id.* at 51,738-39; Exec. Order no. 13258, 67 Fed. Reg. 9385, 9385 (Feb. 28, 2002). If any planned significant regulatory action conflicts with another agency's policy or planned actions, is inconsistent with the priorities of the President of the United States, or is not required by law, necessary to interpret law, or made necessary by compelling public need, then the Director of OMB "may consult with the hea[d] of [the] agenc[y] with respect to [its] Plans, and, in appropriate instances, request further consideration . . . ." Exec. Order no. 12866, 58 Fed. Reg. at 51,739; Exec. Order no. 13258, 67 Fed. Reg. at 9385.

The Executive Order defines significant regulatory actions as those that, among other things, may "[h]ave an annual effect on the economy of $100 million or more or adversely affect in a material way the economy, a sector of the economy, [or] . . . public health or safety." Exec. Order no. 12866, 58 Fed. Reg. at 51,738. Many types of devices that reach the market by means of a substantial equivalence order result in $100 million of business or more annually for manufacturers, distributors, and others in the health sector of the economy. Compound the value of the specific device by all substantially equivalent devices that could be affected by a rescission order and, even if the agency issues only a single rescission order in a year, the potential to exceed $100 million annually is likely.

The Executive Order also defines significant regulatory actions as those that "[r]aise novel legal or policy issues arising out of legal mandates, . . . or the principles set forth in this Executive [O]rder." *Id.* One principle enumerated in the Executive Order is that each agency "shall avoid regulations . . . that are inconsistent, incompatible or duplicative with its other regulations . . . ." *Id.* at 51,736. As discussed below, rescission would duplicate, although without adequate protections, many of the enforcement authorities available to FDA under the FD&C Act, and of course, the FD&C Act's reclassification provisions. Because 510(k) rescission is not authorized by the FD&C Act, and relates to a complex classification/marketing clearance question, any FDA regulation addressing or proposing rescission would be significant.

As amended, the Executive Order requires each agency to identify the "specific market failure . . . or other specific problem that it intends to address . . . that warrant new agency action, as well as assess the significance of [the] problem, to enable assessment of whether any new regulation is warranted." Exec. Order no. 13422, 72 Fed. Reg. 2763, 2763 (Jan. 23, 2007). As explained below, FDA does not need to rescind 510(k)s in order to protect the public health by removing predicate devices from use. As a result,

this new agency action could not be reasonably justified under the Executive Order. In light of yet another Executive Order requirement – to "assess the costs and benefits of the intended regulation, and . . . propose or adopt a regulation only upon a reasoned determination that the benefits of the intended regulation justify its costs" – a rescission regulation should not go forward. Exec. Order no. 12866, 58 Fed. Reg. at 51,736. As discussed above, the costs of rescinding a premarket notification could be quite substantial because not only would the rescinded 510(k) device be affected, but each and every device that claimed the device as a predicate would be affected.

In sum, a regulation establishing rescission of classification determinations would require substantial and costly procedural protections and compliance with Executive Order number 12866 (as amended) that would require that the cost of a rescission regulation be justified by a benefit, assuming authority exists to promulgate and enforce such a regulation. Because inappropriate predicates can be removed from use through administrative or judicial means at considerably less expense than a rescission proceeding that could implicate numerous devices and persons, a rescission regulation could not be reasonably justified in the context of the Executive Order.

V. FDA DOES NOT NEED TO RESCIND A 510(K) CLEARANCE TO PROTECT THE PUBLIC HEALTH.

Although the FD&C Act does not provide FDA with the authority to rescind 510(k)s, it does provide several other means through which the government can remove an unsafe or violative product from the market, and thus, eliminate those products as predicates in the premarket notification process. FDA does not need 510(k) rescission to protect the public health.

For example, under the FD&C Act, the government has express authority to remove devices from commercial distribution and use through the Act's injunction and seizure authority upon demonstrating, by a preponderance of evidence, that a device is adulterated or misbranded, *see* §§ 332 & 334. The government can also effectively remove a device from the market through its replacement authority. *See* FD&C Act § 518(b). Moreover, the FD&C Act provides FDA with very powerful administrative remedies to protect the public health, including mandatory recall authority, *see* § 518(e) (authorizing a recall of any device that presents a reasonable probability of "serious, adverse health consequences or death") and the authority to promulgate a regulation to ban a device, *see* § 516 (if "a device intended for human use presents substantial deception or an unreasonable and substantial risk of illness or injury" and the manufacturer does not comply with the agency's request to correct or eliminate the risk through labeling).[1]

[1] Removal from the market of a device by FDA, and a judicial order of misbranding or adulteration, will result in the elimination of a predicate when the action would prohibit the re-introduction of the device into commerce. In other words, devices that can be reconditioned without new 510(k)s, e.g., if a device is enjoined from a distributor because of Good Manufacturing Practice (GMP) violations, once GMP-

The agency can use its express statutory authority under the FD&C Act to obtain a court's determination of misbranding or adulteration, or device replacement order. These outcomes would eliminate devices from being predicates, *see id.* § 513(i)(2), without the need for additional authorities. In other words, if there is something violative or dangerous about a specific device, the remedy is an action against the device or device owner and not against the "type of device" classified under section 510(k).

VI. THE GROUNDS PREVIOUSLY ASSERTED BY FDA FOR RESCISSION AUTHORITY DO NOT PROVIDE LEGITIMATE BASES TO RESCIND SUBSTANTIAL EQUIVALENCE ORDERS.

In a 2001 proposed rule, FDA asserted six grounds as bases to rescind 510(k) classification orders. *See* 66 Fed. Reg. 3523, 3524-25 (Jan. 16, 2001). None of these grounds necessitate the conclusion that a substantial equivalence order should be revoked. Several of the grounds previously relied upon by FDA permit a change in classification because the agency has altered its standards for making a substantial equivalence determination for a type of device. Other grounds for rescission asserted in the agency's 2001 proposal are deficient because, even assuming their presence, it does not follow that rescission would be the appropriate remedy. In sum, none of these justifications in 2001 or now justify rescission.

VI. CONCLUSION.

FDA does not have express or implied statutory authority to rescind 510(k) classification determinations, nor are there compelling policy grounds to do so. We agree that FDA can nullify a substantial equivalence determination, if the 510(k) submitter procured the determination through fraud, or if the agency made an inadvertent administrative mistake or error and corrected it prior to the order becoming final. Rescinding one 510(k) clearance could potentially reclassify a group of devices, and FDA does not need to take such action in order to protect the public health. The FD&C Act provides the agency with numerous efficient means to remove unsafe or violative devices from the market, and eliminate them as predicates. Moreover, the FD&C Act authorizes FDA to reclassify devices based on new information, including reassessment of past information in the administrative record. The Working Group indicated that rescission would be seldom used in response to particular circumstances; we believe the law now provides adequate remedies for any such circumstance and fully provides adequate protection of the public health if the agency is willing to use the remedies Congress gave it to ensure safe and effective devices.

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compliant, the device is no longer adulterated and therefore could be marketed without any change to the device. Section 513(i)(2) is intended to eliminate predicates when the device cannot be re-introduced into commerce under its past clearance authority, *i.e.*, when modifications to the device to make it lawful would require a 510(k).

ATTACHMENT C

AdvaMed
Advanced Medical Technology Association

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
Advanced Medical Technology Association

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.

AdvaMed
Advanced Medical Technology Association

COMPARISON OF ADVAMED AND CDRH 510(k) WORKING GROUP RECOMMENDATIONS
CLASS II SUBSET

PROPOSAL/ RECOMMENDATION	ADVAMED	CDRH WORKING GROUP	COMPARISON
Identification of a new subset ("Class IIb") for which more expansive data requirements will exist	Identification of ***small, focused, and dynamic subset*** of Class II devices subject to a sub-tier of regulation for which additional submission and postclearance requirements would apply to adequately evaluate the substantial equivalence of the device	Create "Class IIb," subset of Class II devices for which enhanced clinical information, manufacturing information, and/or additional postmarket evaluation would typically be necessary to support a substantial equivalence determination	AdvaMed's proposal does not contemplate and does not agree with the creation of a new class of devices ("Class IIb"). AdvaMed's proposal refers to a more limited and dynamic subset of Class II devices.
Statutory requirements re: new subset	Limited and fits within current classification scheme; does not require statutory change	FDA claims that creation of a new Class IIb is within the scope of the current, three-tiered device classification system established by statute	FDA may not have the statutory authority to create a Class IIb without new legislation.
Breadth of subset	Implantable, life-sustaining devices, and/or life-supporting devices; NOT included IF devices have well-characterized uses and technologies; a record of safety in clinical use; or up-to-date and effective standards, guidance, and/or special controls	Implantable, life-sustaining devices, and/or life-supporting devices (greater risk than other Class II devices); IVDs	Public FDA comments suggest Class IIb contemplated is more expansive than AdvaMed's proposed subset and could include all devices for which clinical data already are required (i.e., IVDs).
Identification of devices to include in subset	• Device types with higher level of concern associated with intended use or new technology using risk management processes; • FDA to publish list in Federal	Aug. 31 Webinar: • Shuren: ". . . the establishment of Class IIb category is a mechanism by which we're looking to otherwise	The types of devices contemplated for enhanced requirements are similar, but public comment indicates that FDA's list likely would be more expansive and less subject to change over time.

PROPOSAL/ RECOMMENDATION	ADVAMED	CDRH WORKING GROUP	COMPARISON
	Register for comment; and • Once well-established with history of safe use, remove from list	downclassify Class III devices." • Includes IVDs	
Enhanced premarket requirements	• Device-specific technical bench testing • Clinical data (when animal and bench are insufficient), including published and/or unpublished reports of device or closely related device • Device-specific additional evidence of safety and effectiveness • Flow chart summary of manufacturing and controls	• Clinical data (least burdensome alternatives not discussed) • Manufacturing process and design control information • Aug. 31 webinar: The Agency recommended pre-IDE meetings to establish clinical study requirements for Class IIb devices.	As compared to the Working Group, AdvaMed's proposal contemplates alternative forms of clinical data, when necessary; device-specific nonclinical testing to support safety and effectiveness; and less extensive manufacturing information.
Post-clearance requirements	Post-clearance periodic reports (case-by-case) for design changes; labeling changes; postclearance experience; other updates	• Greater authorities to require postmarket surveillance/ condition-of-clearance studies • UDI system • Regular, periodic reports of modifications made without submission of a new 510(k)	AdvaMed did not propose enhanced postmarket surveillance or "condition-of-clearance" studies.
Labeling	Submission to FDA of final instructions for use at time of market introduction.	Regular, periodic updates to labeling. Labeling updates will be screened by FDA and posted to a public database.	AdvaMed did not propose placement of final labeling in a public FDA database.
Pre-clearance inspections	Not proposed	Proposed (with the intention of withholding clearance for	AdvaMed did not propose withholding clearance or pre-

PROPOSAL/ RECOMMENDATION	ADVAMED	CDRH WORKING GROUP	COMPARISON
		noncompliance with QSR if potential for serious health risk)	clearance inspections.