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<u>CDRH PRELIMINARY INTERNAL EVALUATIONS – VOLUME II</u>

Task Force on the Utilization of Science in Regulatory Decision Making

Preliminary Report and Recommendations

August 2010

Center for Devices and Radiological Health

U.S. Food and Drug Administration

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1. EXECUTIVE SUMMARY

The Center for Devices and Radiological Health (CDRH or the Center) within the U.S. Food and Drug Administration (FDA or the agency) uses science to guide its regulatory decision making across the total product life cycle of medical devices and radiation-emitting products.[1] At any stage of that life cycle, CDRH may encounter new, unfamiliar, or unexpected scientific information that may influence its thinking, expectations, and actions. To fulfill its mission to protect and promote the public health, the Center must strike a balance between the ability to adapt its approach as new science emerges, and the desire to provide predictable regulatory pathways that foster innovation.

The Task Force on the Utilization of Science in Regulatory Decision Making (the Task Force) was convened in September 2009 to review how CDRH uses science in its regulatory decision making process, and to make recommendations 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.[2]

The Task Force was comprised of representatives from across the Center. As part of its assessment, the Task Force gathered input from CDRH employees and managers (*hereinafter* staff) and a range of external constituencies on how the Center currently uses scientific information to support its regulatory work, what challenges it faces, and what steps it might take to improve its effectiveness in protecting and promoting the public health.[3] This preliminary report is the product of the Task Force's efforts.

1.1. Overview of Findings and Recommendations

The recommendations contained in this report are preliminary. FDA has not made any decisions on specific changes to pursue. FDA is soliciting public input on the recommendations discussed in this report, including the feasibility of implementation and potential alternatives. Once its assessment of public input and other necessary reviews are completed, FDA will announce which improvements it will implement, as well as projected timelines for implementation.

The incorporation of new science into CDRH's decision making depends on three major elements. First, to enhance its science-based decision making generally, the Center must have adequate scientific understanding, based on meaningful, high-quality, up-to-date information, analytical and technical expertise, and an operational and organizational infrastructure that supports knowledge-development and knowledge-sharing. Second, to determine the appropriate action(s) to take when faced with new science — including, potentially, deciding to take no immediate action — the Center should apply an approach that provides as much predictability as practical and that is consistent with its authorities. Third, when it has decided to take a particular action, the Center should communicate its decision and its rationale promptly and as broadly as permissible.

The Task Force identified several areas for improvement related to each of these elements.

[1] Some medical devices (namely, those related to the diagnosis of retroviruses such as HIV, and those related to blood, human tissue, and cellular products) are under the jurisdiction of FDA's Center for Biologics Evaluation and Research (CBER). This document pertains only to CDRH.

[2] *See* Section 3.1 of this report for the Task Force's working definition of "new science."

[3] Although the Task Force sought input from a wide range of CDRH staff and external constituencies, there may be perspectives that it did not hear and that therefore are not reflected in this preliminary report.

With regard to CDRH's scientific knowledge base, the Task Force found that it is difficult for Center staff to efficiently and effectively obtain complete information about the risks and benefits of regulated products across the total product life cycle. This can lead to unnecessary delays and burdens during premarket review and make it challenging for the Center to identify and respond to postmarket trends quickly and appropriately. The Task Force recommends that CDRH take proactive steps to improve the quality of premarket data, particularly clinical data; address review workload challenges; and develop better data sources, methods, and tools for collecting and analyzing meaningful postmarket information.

In addition, the Task Force found that it is difficult for CDRH staff to share scientific knowledge across the Center, in part due to staffing limitations, and to tap meaningful external scientific expertise in a timely manner. The Task Force therefore recommends that the Center conduct an assessment of its staffing needs to accomplish its mission-critical functions and prepare for anticipated scientific challenges. The Task Force also recommends that CDRH take steps to improve knowledge management within the Center and make better use of experts outside of the Center, in part by developing a web-based network of external experts, using social media technology.

With regard to determining the appropriate action(s) to take when faced with new science, the Task Force found that CDRH has not yet articulated a business process to be followed across the Center for evaluating new scientific information and determining when that information warrants certain types of action, such as a change in premarket evidentiary expectations. As a starting point for discussion and comment, the Task Force developed a conceptual framework for such a process, 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. The Task Force also identified a few key principles that should be considered as the Center puts this framework into practice. Most notably, the Task Force recommends that CDRH establish a Center Science Council, comprised of experienced employees and managers and under the direction of the Deputy Center Director for Science, to help assure consistency across the Center in responding to new scientific information.

Finally, the Task Force found that, when new scientific information changes CDRH's regulatory thinking, it is challenging for the Center to communicate the change and its basis to all affected parties in a meaningful and timely manner. The Task Force recommends that, in addition to continuing its ongoing efforts to streamline guidance development, the Center make use of more rapid tools for broad communication on regulatory matters. For example, CDRH should establish as a standard practice sending open "Notice to Industry" letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations on the basis of new scientific information. CDRH should adopt a uniform template and terminology for such letters, including clear and consistent language to indicate that the Center has changed its regulatory expectations, the general nature of the change, and the rationale for the change. CDRH 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.[4] Where appropriate, such letters should be followed as quickly as possible by new or revised

[4] Under FDA's Good Guidance Practices regulation and consistent with section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (21 USC §371(h)(1)(C)), Level 1 guidance documents may be implemented without FDA seeking prior comment if the agency determines that prior public participation is not feasible or appropriate, such as when immediate implementation is necessary to protect the public health. 21 CFR 10.115(g)(2). FDA will invite comments at the time of issuance of such guidance,

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 regulatory thinking. The Task Force also recommends that CDRH continue ongoing efforts to increase the transparency of its decision making processes and rationale, in order to clarify the basis for any action it takes in response to new scientific information.

The Task Force's findings and recommendations are outlined on the following pages and discussed in greater detail in Section 4 of this report. Terms used in the box below are explained in the body of the report. Additional information about the Task Force's work, including a summary of staff and public input, is provided in the Appendices.

and, if the agency receives comments, FDA will review those comments and revise the guidance when appropriate. 21 CFR 10.115(g)(3).

Overview of Findings and Recommendations

1. Enhancing CDRH's Scientific Knowledge Base

» **Finding:** Challenges related to CDRH's current data sources, methods, and administrative practices make it difficult for the Center to efficiently and effectively obtain complete information about the risks and benefits of regulated products across the total product life cycle.

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**
    - 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.
  - **Quality of Clinical Data**
    - The Task Force recommends that CDRH continue its ongoing efforts to improve the quality of the design and performance of clinical trials used to support premarket approval applications (PMAs), 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.
    - 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.

- **Review Workload**
  - ➢ 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.
  - ➢ 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.

- ***Postmarket Oversight***
  - ➢ 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.

» **Finding:** Limitations in CDRH's current staffing levels, training, and knowledge management infrastructure make it challenging to share scientific knowledge across the Center and to develop new knowledge from available information sources.

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

- ➢ 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 devices to Center staff in a readily comprehensible format, to efficiently and effectively support their day-to-day work.

» **Finding:** It is difficult for Center staff to tap meaningful external scientific expertise in a timely manner.

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

- The Task Force recommends that CDRH, consistent with the Center's FY 2010 Strategic Priorities, develop a web-based network of external experts, using social media technology, in order to appropriately and efficiently leverage external expertise that can help Center staff better understand novel technologies, address scientific questions, and enhance the Center's scientific capabilities.
- The Task Force 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.

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

» **Finding:** 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 expectations.

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.

- 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.

- 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.

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

» **Finding:** As CDRH incorporates new science into its decision making, it is difficult for the Center to communicate its current or evolving regulatory thinking to all affected parties in a timely and meaningful manner.

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

- 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.
- 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.[5] 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.

- 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).

» **Finding:** There has been a lack of transparency about the Center's rationale for taking a particular course of action in response to new science.

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.

- 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.

[5] Under FDA's Good Guidance Practices regulation and consistent with section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (21 USC §371(h)(1)(C)), Level 1 guidance documents may be implemented without FDA seeking prior comment if the agency determines that prior public participation is not feasible or appropriate, such as when immediate implementation is necessary to protect the public health. 21 CFR 10.115(g)(2). FDA will invite comments at the time of issuance of such guidance, and, if the agency receives comments, FDA will review those comments and revise the guidance when appropriate. 21 CFR 10.115(g)(3).

- 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.

2. BACKGROUND AND GOALS

CDRH uses science to guide its regulatory decisions, from premarket approval and clearance through postmarket oversight and compliance actions. Science and technology are constantly changing over time, particularly in the world of medical devices. Devices are unique among medical products in that they are defined by innovation, either through incremental evolution or disruptive revolution. In addition, CDRH's oversight of the products it regulates spans the total product life cycle, from the early stages of product conception and development through market use. Long-term experience with products on the market — even when the products themselves remain unchanged — can provide new, scientifically significant information that was not previously available to the Center.

In order for CDRH to fulfill its mission to protect and promote the public health, the Center's regulatory decision making process must be able to adapt as science evolves and as new information emerges about the risks or benefits of a given product. As CDRH's knowledge and that of the broader scientific community change, the Center must be prepared to change its course as necessary to uphold its responsibility to the public. CDRH already deals with this challenge regularly, and it typically makes adjustments to its work and its expectations on a case-by-case basis. The Center has a number of regulatory and non-regulatory tools it uses to respond to new and evolving science, ranging from formal or informal communications to compliance actions or regulatory changes.

However, CDRH also recognizes that, in order to foster innovation, generally minimize burdens on industry without compromising patient safety, and use Center resources most efficiently, it needs to provide industry and Center staff with as much predictability as practical in its regulatory pathways.

In September 2009, a Center-wide Task Force on the Utilization of Science in Regulatory Decision Making was convened to identify steps CDRH should take to balance the ability to adapt readily to new and evolving science and the desire for predictability. The group was charged to assess the way the Center currently anticipates and responds to new and evolving science in its regulatory decision making, and to recommend improvements.[6]

The central goal of the Task Force was to help CDRH become more "predictably adaptive": to set clearer guidelines about when new scientific information would lead the Center to take a particular course of action, and to determine how the Center should communicate its thinking in such situations to its external constituencies, in order to maintain as much consistency and transparency as practical. A second and related goal was to identify proactive steps the Center should take to stay abreast of new scientific developments that might influence its thinking, and reduce uncertainty and gaps in knowledge to enhance its science-based decision making.

[6] *See* Appendix A for the Task Force's charge from the Center Director.

3. TASK FORCE METHODS

3.1. Scope of Work

The Task Force began its work by better defining the boundaries of its charge from the Center Director. The first part of this effort was to develop a working definition of the term "new science," described in the charge as follows: "*New science* refers to new data about the risk/benefit profile[7] of devices; new information about manufacturing practices and processes; new scientific fields and technologies, such as nanotechnology; and new regulatory science, including analytic, tools."[8]

The Task Force grouped these elements into three major categories of scientific developments that could influence the Center's thinking and expectations: (1) evolving information; (2) novel technologies; and (3) new scientific methods to support decision making. Each of these categories may present different types of questions and challenges for the Center, as illustrated in the box below.

"New Science": A Working Definition

Evolving Information. CDRH's oversight of medical devices spans the total product life cycle, from early development through long-term experience with devices on the market. At any point in the life cycle of a given device, new information may come to light that was not previously available to the Center. Examples of evolving information include new data that alter the Center's understanding of a device's risks and/or benefits, new information about a company's manufacturing practices, and incremental changes in the design of second- or later-generation devices. The emergence of new information about a device or group of devices[9] may lead the Center to take a particular course of action. Depending on the situation, the Center may, for instance, issue a public communication, provide feedback to manufacturers, initiate a study to learn more, take an enforcement action, or adjust its regulatory treatment of that device or other devices in the same group (*e.g.*, through establishment of special controls).

Novel Technologies. CDRH is at times faced with a new type of technology, or a novel use of an existing technology, with which it has limited or no experience. Examples of novel technologies include nanotechnology and advances in medical robotics. Due to uncertainty about their benefits and risks, novel technologies may warrant a different type or level of evidence for premarket review and/or postmarket surveillance than well-understood technologies.

New Scientific Methods to Support Decision Making. The development of new methods and/or tools for data gathering and/or analysis may allow CDRH to draw scientific conclusions from data of

[7] The term "risk/benefit profile" is used throughout this report to refer generally to the current understanding of the risks and benefits of a given device for specific uses and user populations. A change in the risk/benefit profile of a device is a change in understanding of the device's risks and/or benefits, even if that change is not severe enough to cause the risks, in general, to outweigh the benefits. For example, information that calls into question the certainty of a risk/benefit assessment could result in a change in the risk/benefit profile.

[8] *See* Appendix A for the full charge from the Center Director.

[9] The term "group of devices" or "device group" is used throughout this report to refer to a set of devices that share common characteristics. A group of devices might be, for example, a given device type (*e.g.*, insulin infusion pumps), a device family (*e.g.*, all types of infusion pumps), a set of devices that share a common cross-cutting feature (*e.g.*, wireless devices or devices that rely on software), or a set of devices that share a common cross-cutting use environment (*e.g.*, home use devices). A device of a particular brand and model is described in this report using the term "device model" or "model."

a different type, or from a different source, than had previously been possible. Examples of new methods to support decision making include the application of Bayesian statistics to clinical trials, data mining of spontaneous adverse event reports, computational models for human body function and device performance, scientific computing, new biomarkers, and active surveillance study designs using observational data based on electronic health record systems. The development of new methods may allow for a change in the Center's regulatory expectations. There has been discussion, for example, about the extent to which "real-world" clinical data (*e.g.*, anonymized data on device use and outcomes pooled from electronic health record systems) could be used in support of future premarket submissions.

In addition to defining "new science," the Task Force determined how to circumscribe its work in relation to other ongoing initiatives at CDRH that shared elements of its charge. The 510(k) Working Group, for example, was tasked, in part, with assessing the consistency of the Center's decision making within the context of the medical device premarket notification, or 510(k), review process.[10] The Task Force broadly interpreted the term "regulatory decision making" in its charge to encompass actions the Center might take at any point in a regulated product's life cycle — including but not limited to premarket decisions. The Task Force decided that where its charge touched on an issue that was specifically being addressed by another more narrowly focused group, as in the case of the 510(k) Working Group or any other project listed as part of the Center's FY 2010 Strategic Priorities,[11] it would defer to that group. At various points in this report, therefore, the Task Force refers to other such projects.

Finally, the Task Force considered what the nature of its recommendations should be. The group decided that it would discuss a range of options for the Center, including administrative, regulatory, and statutory changes that the Center might pursue to improve the way it incorporates new and evolving science into its decision making. However, in an effort to put forward recommendations that are realistic and actionable, the Task Force agreed to focus primarily on steps the Center could take using its existing authority and resources.

3.2. Staff Participation

As a Center-wide initiative, the Task Force was comprised of representatives from across CDRH. To allow for broader staff input, the group solicited information from individuals across CDRH through a series of focus group interviews in October and November 2009. The groups were selected to represent a range of perspectives within the Center, spanning multiple Offices, organizational levels, and scientific content areas.[12]

In an effort to collect additional input from Center employees, the Task Force co-hosted a staff-wide internal town hall meeting on February 24, 2010, in conjunction with the 510(k) Working Group. The Task Force also invited Center staff to provide written comments on its ongoing work through a web-based social media tool.[13]

[10] *See* "CDRH Preliminary Internal Evaluations – Volume I: 510(k) Working Group Preliminary Report and Recommendations." Available at http://www.fda.gov/FDAgov/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM220272.

[11] "CDRH FY 2010 Strategic Priorities." Available at http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHVisionandMission/ucm197647.htm.

[12] *See* Appendix B for a list of the groups interviewed.

[13] *See* Appendix B for a summary of staff feedback.

3.3. Public Comment

To gather input from CDRH's external constituencies, the Task Force held a public meeting on February 9, 2010.[14] The group also collected written comments through a public docket that was open from December 18, 2009 through February 24, 2010.[15]

[14] *See* Appendix C for a summary of the public meeting.
[15] *See* Appendix D for a summary of the written comments.

4. FINDINGS AND RECOMMENDATIONS

The incorporation of new science into CDRH's decision making is predicated on three major elements. First, to enhance its science-based decision making generally, the Center must have adequate scientific understanding, based on meaningful, high-quality information, analytical and technical expertise, and an operational and organizational infrastructure that supports knowledge-development and knowledge-sharing. Second, to determine the appropriate action(s) to take when faced with new science — including, potentially, deciding to take no immediate action — the Center should apply an approach that provides as much predictability as practical and that is consistent with its authorities. Third, when it has decided to take a particular action, the Center should communicate its decision and its rationale promptly and broadly.

Through its discussions with Center staff and external constituencies, the Task Force made several key findings and recommendations regarding each of these elements.

4.1 Enhancing CDRH's Scientific Knowledge Base

In order for CDRH to respond appropriately to new science using a rational, risk/benefit-based approach, the Center must first have an adequate understanding of the situation at hand. CDRH's decision making is guided by scientific information it obtains from a variety of sources, including but not limited to premarket submissions, adverse event reporting, in-house or published scientific studies, and partnerships with other science-driven organizations. However, due to limitations in CDRH's current data sources and analytic methods, as well as limitations in the Center's ability to take full advantage of internal and external information and expertise, CDRH's understanding of the risks and benefits of a given product at different stages of its life cycle may be less complete than it otherwise could be. As discussed further below, these limitations hinder the Center's ability to establish, evaluate changes in, and make as fully informed decisions as possible based on the risk/benefit profile of its regulated products in a predictable, transparent, and timely manner. While it is not possible to eliminate uncertainty entirely, there are actions that the Center should take to reduce uncertainty and enhance its science-based decision making.

4.1.1. Finding: Challenges related to CDRH's current data sources, methods, and administrative practices make it difficult for the Center to efficiently and effectively obtain complete information about the risks and benefits of regulated products across the total product life cycle.

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

4.1.1.1. Premarket Review

With the exception of certain lower-risk devices that are exempt from premarket review, CDRH reviews the safety and effectiveness of devices for their intended use on the basis of available information. Under the premarket approval (PMA) process, each manufacturer must independently demonstrate reasonable assurance of the safety and effectiveness of its device for its intended use.[16] Under the

[16] Under 21 CFR 860.7(d)(1), there is a *reasonable assurance of safety* "when it can be determined, based upon valid scientific evidence, that the probable benefits to health from the use of the device for its intended uses and conditions of use,

premarket notification (510(k)) process, CDRH will clear a device if it finds, through review of a 510(k) submission, that the device is substantially equivalent to a predicate device. Generally, predicate devices, as largely class II devices, are those for which there is a reasonable assurance of safety and effectiveness with general and applicable special controls.[17]

Due to the fact that there is inherently limited information about and experience with devices that have not yet been marketed, there is some level of unavoidable and generally acceptable uncertainty about the safety and effectiveness of a device under premarket review. The Center's understanding of the device's risk/benefit profile will mature throughout the course of the device's life cycle, as it is used in a broader patient population and over a longer timeframe. Therefore, CDRH's regulatory treatment of the device may inevitably change over time. Even with these acknowledged limitations, however, the information provided during premarket review must still be sufficient to allow for a well-supported decision.

According to Center staff, challenges related to CDRH's current policies, practices, and premarket workloads can make it difficult for the Center to predictably and efficiently obtain and assess sufficient information about the risks and benefits of devices under review. As discussed further below, these challenges can lead to potentially avoidable delays in the review process for both Center staff and industry.

Interpretation of the "Least Burdensome" Provisions. One factor that contributes to this issue is the broad application of the so-called "least burdensome" provisions of the Federal Food, Drug, and Cosmetic Act (FDCA). Section 513(a)(3)(D)(ii) of the FDCA[18] states, "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) of the FDCA[19] states, "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 a request, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly." These provisions were added to the FDCA under the Food and Drug Administration Modernization Act of 1997 (FDAMA).[20]

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when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks." Under 21 860.7(e)(1), there is a *reasonable assurance of effectiveness* "when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

[17] *See* 21 CFR 860.3(c)(2).

[18] 21 USC §360c(a)(3)(D)(ii).

[19] 21 USC §360c(i)(1)(D).

[20] Pub. L. No. 105-115, 111 Stat. 2296.

In 2002, CDRH issued a guidance document that put forth a broad interpretation of these provisions, extending the "least burdensome" principle beyond the two areas specified in the statute.[21] The guidance states:

> The least burdensome concept should be integrated into all premarket activities, as well as postmarket activities as they relate to the premarket arena. These activities include:
>
> - Simple inquiries regarding device development
> - Pre-submission activities, including early collaboration meetings and the pre-IDE process
> - Premarket submissions
> - Panel review and recommendations
> - Post-approval studies
> - Reclassification petitions
> - Guidance document development and application
> - Regulation development[22]

One of the aims of the "least burdensome" provisions was to eliminate *unjustified* burden on industry in the premarket setting, while still maintaining the statutory criteria for device clearance or approval to protect the public health.[23] Similarly, the 2002 guidance states, "In order for the least burdensome approach to be successful, it is important that industry continue to meet all of its statutory and regulatory obligations, including preparation of appropriate, scientifically sound data to support premarket submissions. It is also important that FDA continue to enforce the statutory and regulatory provisions that are in place to protect the public after a device reaches the market."[24] These principles are consistent with good governance in general: if more than one approach will meet the same public health objective and statutory standard, it is reasonable to support the one that is less burdensome.

However, in the 2002 guidance, the term "least burdensome approach" is frequently used without the balancing statement that such an approach still needs to be adequate to fulfill FDA's regulatory requirements. For example, the guidance states, "If industry believes that the Agency did not use the least burdensome approach in attempting to resolve a regulatory issue, there are several avenues available to address this concern."[25] Center staff reported that industry, in turn, has interpreted this language broadly as allowing manufacturers to invoke the "least burdensome" concept in disputes

[21] "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concepts and Principles; Final Guidance for FDA and Industry." Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm.

[22] *Id.* at 2-3.

[23] The Senate Report on FDAMA states, "This amendment of section 513(a)(3) is also intended to carry through the philosophy of the 'Medical Device Amendments of 1976.' Those amendments were committed to avoiding overregulation of devices. Section 301 achieves this laudable goal by requiring that the FDA's specification of the types of evidence to demonstrate reasonable assurance of effectiveness 'result [from] a determination by the [Agency] that such data are necessary to establish device effectiveness and that no other less burdensome means of evaluation [*sic*] device effectiveness is available which would have a reasonable likelihood of resulting in approval.' Simply put, the FDA may not ask for the ultimate study to prove effectiveness. It must ask for the least burdensome type of valid scientific evidence that will meet Congress' criteria for effectiveness. It is Congress' formulation for proving effectiveness that counts. FDA has never had freedom to require evidentiary showings that exceed what is required under the law for an approval. This provision reinforces that fact." S. Rep. No. 105-43, 105th Cong. 1st Sess. (1997), at 25.

[24] "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concepts and Principles; Final Guidance for FDA and Industry," at 2.

[25] *Id.* at 7.

across a range of areas, regardless of whether or not the burden in question is justified from a regulatory perspective.

In comments to the Task Force, CDRH staff expressed concern that the "least burdensome" provisions, as interpreted in the 2002 guidance, have created a culture in which it is difficult for premarket reviewers to efficiently obtain a sufficient level of evidence to consistently provide reasonable assurance of a device's safety and effectiveness. This is particularly challenging in the context of the 510(k) process, in which reviewers report that 510(k) submitters, relying on the substantial equivalence standard, are often reluctant to provide additional information that was not required for a predicate device. Although reviewers may believe they need additional information to address a safety and/or effectiveness concern based on new scientific information that was not available when the predicate was cleared, 510(k) submitters commonly may contest additional information requests as overly burdensome or creating an "uneven playing field."

According to the annual reports of the CDRH Ombudsman, which include information dating back to 2000, concerns about whether or not premarket evidentiary requirements are consistent with the "least burdensome" provisions have consistently been a leading reason for complaints, disputes, and/or inquiries from industry. Concerns related to the "level playing field" concept were among the top five reasons for complaints, disputes, and/or inquiries in eight of the past ten years.[26] Manufacturers have expressed concern that some additional information requests do not immediately appear relevant or necessary. This issue is discussed further in Section 4.3.2 of this 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 FDCA. 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.

Quality of Clinical Data. In addition to the challenges presented by the least burdensome provisions and CDRH's interpretation thereof, questions have been raised both within and outside of the Center about the quality of data, particularly clinical trial data, used in support of premarket submissions. Two recent reports by Center staff and outside researchers, for example, have highlighted shortcomings in clinical trials supporting PMA submissions for certain cardiovascular devices.[27,28] Inconsistent quality of clinical trial design and data supporting either PMA or 510(k) submissions can make it difficult for CDRH staff to accurately assess a device's risks and benefits. Because clinical trials are typically very costly, it can be detrimental to a manufacturer if the quality of its clinical trial design and/or data is not sufficient to support clearance or approval. In addition, poor-quality trial design and/or data can prevent promising innovative products from reaching patients.

[26] *See* "CDRH Ombudsman Annual Reports." Available at http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm109765.htm. Annual Reports are available for CY 2001 and CY 2003 through CY 2009. Taken together, these reports include annual data for all years from CY 2000 through CY 2009.

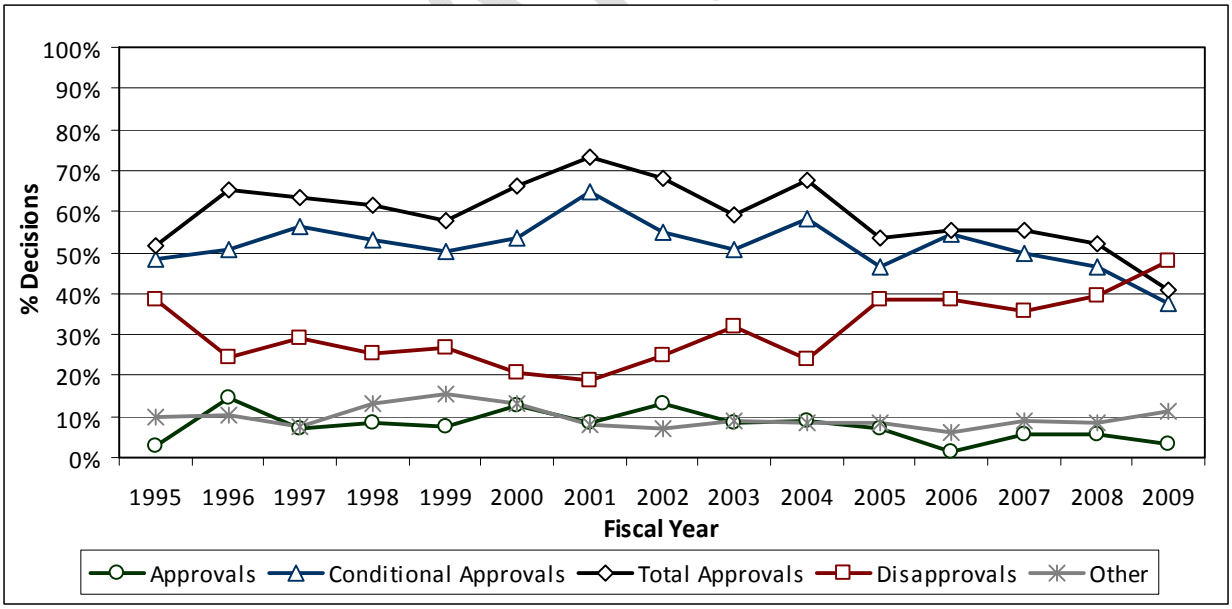
[27] Kramer DB, et al., "Premarket clinical evaluation of novel cardiovascular devices: quality analysis of premarket clinical studies submitted to the Food and Drug Administration 2000-2007," *American Journal of Therapeutics,* January/February 2010, Vol. 17, No. 1, pp. 2-7.

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

CDRH offers manufacturers the option of meeting with Center staff early in the device development process, to discuss the non-clinical and clinical components of their pending premarket submissions. These meetings have historically been called "pre-IDE" meetings, because they sometimes precede the submission of an Investigational Device Exemption application (IDE) and can be used to provide the prospective applicant with advice about any necessary clinical trials. These meetings allow manufacturers that intend to submit certain application types the opportunity to receive feedback from the Center on the type of valid scientific evidence necessary to demonstrate, for the purposes of certain submissions, that the device is effective under the conditions of use proposed by the submitter[29] and — for manufacturers of class III devices — to receive Center feedback on an investigational plan (including a clinical protocol).[30] However, despite the availability and increasing use of these options, CDRH staff have raised concerns about the quality of IDEs and premarket clinical trial data submitted. On the other hand, industry has raised concerns that, in some cases, CDRH may take more time than is appropriate to provide feedback on clinical trial protocols following a pre-IDE meeting or may not provide well-informed feedback on clinical trial protocols, potentially due to insufficient internal expertise and/or a failure to leverage appropriate external expertise.

Figure 4.1, below, shows the percentage breakdown of IDE decisions issued from FY 1995 through FY 2009. The graph shows that, during this time period, IDEs have been frequently disapproved or approved with conditions, and it also evidences an apparent increase in disapproval decisions beginning around 2005. Further analysis will be necessary to determine the causes of or major contributors to these trends. This analysis may consider, among other factors: complexity of submissions; time to reaching a decision; manufacturer experience; the therapeutic area; the manufacturer's use of pre-IDE meetings; and any changes in Center policies over time.

Figure 4.1. IDE Decisions Issued: FY 1995-2009 [31]



[29] Section 513(a)(3)(D)(i) of the FDCA (21 USC §360c(a)(3)(D)(i)).

[30] Section 520(g)(7) of the FDCA (21 USC §360j(g)(7)).

[31] "Approvals" refers to approvals without conditions. "Total Approvals" refers to the sum of "Approvals" (*i.e.*, without conditions) and "Conditional Approvals." "Other" refers to withdrawals, incomplete submissions, and submissions with a pending issue under review by another Center. "Total Approvals," "Disapprovals," and "Other" sum to 100 percent.

- 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 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 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.

- The Task Force further recommends that CDRH work to better characterize the root causes of existing challenges and trends in IDE decision making, including evaluating the quality of its pre-submission interactions with industry and taking steps to enhance these interactions as necessary. For example, the Center should assess whether there are particular types of IDEs that tend to be associated with specific challenges, and identify ways to mitigate those challenges. As part of this process, CDRH should consider developing guidance on pre-submission interactions between industry and Center staff to supplement available guidance on pre-IDE meetings.[32]

Review Workload. Center staff also reported to the Task Force that it is challenging to efficiently complete high-quality premarket reviews given current premarket review workloads and limitations in staffing (as discussed further in Section 4.1.2, below). As shown in Figure 4.2, below, there has been a notable increase in premarket program submissions in recent years. While IDE program submissions have remained relatively stable, PMA program submissions, 510(k) program submissions, and pre-IDE program submissions have all increased markedly. Although staffing levels have also increased slightly during this time period, they have not kept pace with the growing workload. From FY 2005 through FY 2009, there was only a 5.5 percent increase in the number of full-time equivalents supporting the Center's premarket review functions.[33]

Unexpected surges in review workload can lead to delays and make it challenging for staff to meet premarket deadlines[34] and performance goals.[35] In particular, staff reported that it can be difficult to conduct an adequate review of complex clinical trial protocols within the mandated thirty–calendar-day IDE review timeframe, especially when it is necessary to consult with other experts either within or outside of CDRH.

[32] "Early Collaboration Meetings under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff. Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm.

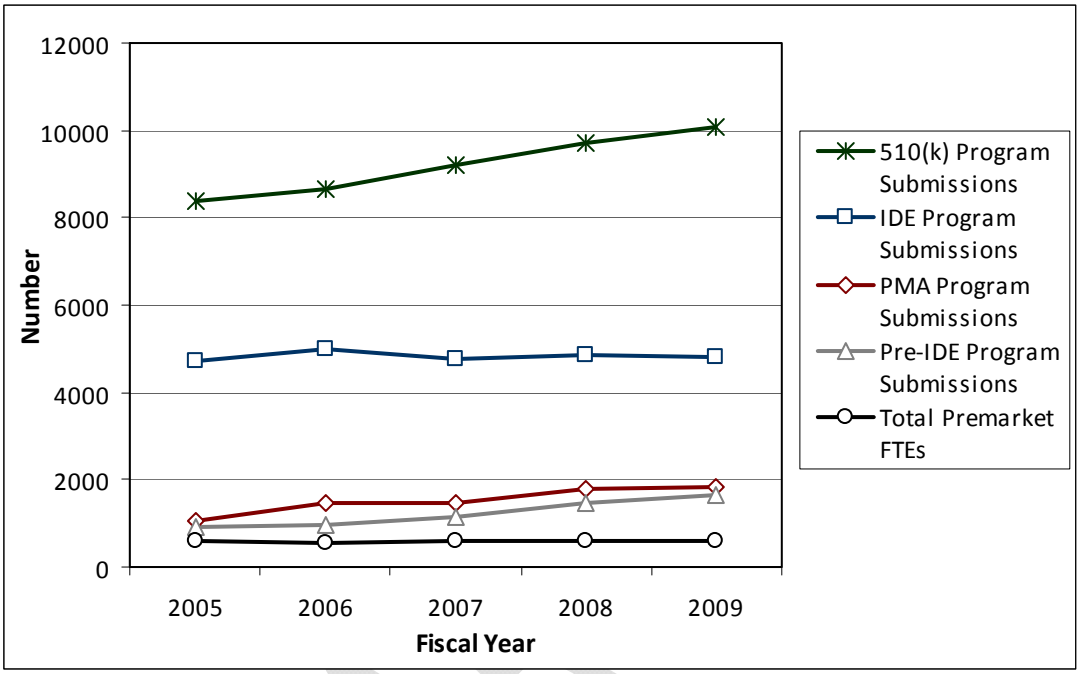
[33] This figure is based on data from the Center's employee time reporting system.

[34] Section 520(g)(4)(A) of the FDCA (21 USC §360j(g)(4)(A)) states that an IDE is "deemed approved on the thirtieth day after the submission of the application to the Secretary unless on or before such day the Secretary by order disapproves the application and notifies the applicant of the disapproval of the application."

[35] CDRH agreed to certain premarket performance goals in a September 27, 2007 letter from former HHS Secretary Michael O. Leavitt to Congress, pursuant to the Medical Device User Fee Amendments of 2007 (MDUFA). The letter, which includes a listing of the Center's performance goals for FY 2008 through FY 2012, is available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/UCM109102.pdf.

In some cases, it has been possible for staff from one review division to temporarily assist with time-critical work in another review division on an ad hoc basis. However, this practice has not been formalized or standardized across the Center's review Offices.

Figure 4.2. Premarket Program Submissions and Full-Time Equivalents: FY 2005-2009 [36]



- 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 in Section 4.1.2, below.

[36] "510(k) Program Submissions" include original 510(k)s, 510(k) amendments ("amendment" refers to any additional information submitted while a 510(k) is under active review by Center staff), 510(k) supplements ("supplement" refers to any additional information submitted while a 510(k) is on hold pending receipt of such information), and 510(k) add-to-file submissions ("add-to-file" refers to any information received after a final decision is made on a given 510(k)). "IDE Program Submissions" include original IDEs, IDE amendments, and IDE supplements. "PMA Program Submissions" include original PMAs, modular PMAs, amendments to original PMAs, and supplements to original PMAs. Note that this figure does not include amendments and supplements to modular PMAs, nor does it include PMA annual reports. "Pre-IDE Program Submissions" include original pre-IDEs and pre-IDE supplements. "Total Premarket FTEs" refers to the end-of-fiscal-year count of all CDRH full-time equivalents supporting premarket review, as documented in the Center's employee time reporting system. Note that Figure 4.2 here shows the number of *all* 510(k)-related submissions received each year, whereas Figures 4.1 and 4.2 in the preliminary report of the 510(k) Working Group show only the number of *original* 510(k)s received.

- The Task Force further 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.

4.1.1.2. Postmarket Oversight

Over the course of a regulated product's life cycle, CDRH builds on the information it obtained in the premarket setting. However, many of the Center's current tools and methods for postmarket oversight are limited to older methods, including passive surveillance systems that rely on mandatory or voluntary adverse event reporting, and older informatics, such as the product code system.[37] These approaches have hampered the Center's ability to capture meaningful risk/benefit information in a timely fashion, particularly as a product's profile evolves over time.

As noted by Center staff and participants at the Task Force's public meeting, medical device adverse event reporting has well-recognized limitations, including various reporting biases, varying reporting practices, and widespread underreporting. In addition, the quality of medical device reports, including the level of detail they contain, is inconsistent. Reports often provide insufficient information to fully assess the adverse event in question, including potential causality. Further, as noted by Center staff and public comments, CDRH does not currently have ready access to meaningful denominator data that could provide insight into device-specific product diffusion, patterns of use, and relative reporting rates.

CDRH's ability to understand a product's postmarket risk/benefit profile has also historically been hampered by a dearth of useful data sources. For instance, many large electronic health-care–related data sources (*e.g.*, from insurers or hospital systems) do not capture and/or integrate device-specific identifiers into health care claims or records.

When CDRH has specific questions about the risks and/or benefits of a marketed product, the Center may order post-approval studies (PAS) as a condition of approval for PMA devices.[38] Alternatively, the Center may order postmarket surveillance studies (also called Section 522 studies, after the section of the FDCA that authorizes them) for class II or class III devices to address certain issues of public health importance,[39] or as a condition of clearance or approval for devices anticipated to have significant use in pediatric populations.[40] Although PAS provide valuable information, they may potentially be limited in size and scope, in part as a consequence of the Center's broad interpretation of the least burdensome provisions, described above. In addition, these studies have had limited success with long-term follow-up. Section 522 studies have historically used more varied approaches to gathering information than PAS, but they may also be limited in size and scope, including statutory limits to study length (specifically, no more than 36 months except when the manufacturer agrees to a longer-term study or, in certain circumstances, if the device is expected to have significant use in pediatric populations).[41] The Center's lack of statutory authority to require Section 522 studies as a condition of clearance, except in

[37] The product code system is discussed further in the preliminary report of the 510(k) Working Group.

[38] Section 522(a)(1)(B) of the FDCA (21 USC §360l(a)(1)(B)).

[39] Section 522(a) of the FDCA (21 USC §360l(a)). Specifically, FDA has the authority to require a manufacturer to conduct postmarket surveillance of a class II or class III device that meets any of the following criteria: (i) its failure would be reasonably likely to have serious adverse health consequences; (ii) it is expected to have significant use in pediatric populations; (iii) it is intended to be (I) implanted in the body for more than one year; or (II) it is a life-sustaining or life-supporting device used outside a device user facility.

[40] Section 522(a) of the FDCA (21 USC §360l(a)).

[41] Section 522(b) of the FDCA (21 USC §360l(b)).

the case of such devices expected to have significant use in pediatric populations, is addressed in further detail in the preliminary report of the 510(k) Working Group.

As mentioned in the CDRH FY 2010 Strategic Priorities, the Center is taking steps to optimize collection and analysis of postmarket data. For example, CDRH has been and continues to be engaged in efforts to promote and facilitate the establishment and use of medical device registries, which can help fill important information gaps for certain device groups. The Center already has access to several device registries, and it is working to facilitate the development of more. However, registries, although useful, are not optimal or feasible for every device group. In addition, even where registries do add value, registry data are generally limited to short-term follow-up (up to 30 days).[42]

A broader and more promising, although longer-term, approach to improving postmarket oversight is CDRH's effort to establish a unique device identification (UDI) system. When incorporated into various internal and external data sources, UDI will facilitate such activities as adverse event reporting and analysis and device recalls, in part by allowing for a greater level of specificity in postmarket oversight than is currently possible using the Center's product code system alone. Furthermore, incorporating UDIs into existing, large-scale electronic health care data systems, such as electronic health records and claims data sets, would allow CDRH and others, for the first time, to use these sources for device-model-specific safety surveillance and observational study. In addition, once these electronic health-related information systems mature and incorporate UDI, it may be possible to use anonymized information generated from "real-world" experience to reduce other evidentiary requirements for future premarket submissions. The Center recognizes, however, that a UDI system will take time to fully implement, and improved approaches to accessing and using information about devices are needed now.

CDRH is also engaged with other stakeholders in efforts to develop a national infrastructure and methodological capabilities to significantly enhance its access to postmarket data and its analytic approaches. FDA leads the Sentinel Initiative, an effort to develop active surveillance capabilities,[43] and the Medical Device Epidemiology Network (MDEpiNet) initiative to develop an academic consortium to focus on epidemiological device issues and methods (*e.g.*, methods and analytic tools for evidence synthesis).[44] In addition, FDA is involved in the Partnership in Applied Comparative Effectiveness Science (PACES), an initiative aimed at enhancing the use of clinical trial and related data for comparative effectiveness research, and efforts related to quantitative decision analysis as applied to medical devices.

- 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 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 (*e.g.*, those noted above, as well as the development of international and domestic standards and the Nationwide Health Information Network[45]). As CDRH continues its efforts to develop better data sources, methods, and tools, it

[42] There are some exceptions to this general limitation in follow-up time, the most common of which are manufacturer-sponsored long-term registries established to fulfill FDA-ordered post-approval study requirements.

[43] *See* "FDA's Sentinel Initiative." Available at http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm.

[44] *See* "Medical Device Epidemiology Network: Developing Partnership Between the Center for Devices and Radiological Health and Academia; Public Workshop," 75 Fed. Reg. 56 (Mar. 24, 2010), pp. 14170-14171. Available at http://edocket.access.gpo.gov/2010/pdf/2010-6446.pdf.

[45] *See* "Nationwide Health Information Network (NHIN): Overview." Available at http://healthit.hhs.gov/portal/server.pt?open=512&mode=2&cached=true&objID=1142.

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.

4.1.2. Finding: Limitations in CDRH's current staffing levels, training, and knowledge management infrastructure make it challenging to share scientific knowledge across the Center and to develop new knowledge from available information sources.

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

To ground their science-based decision making, Center staff sometimes need to consult with experts in scientific areas with which they themselves are not fully familiar, including novel scientific fields. Staff throughout the Center reported to the Task Force that it is difficult to identify and access in-house experts in specific areas.

This difficulty is in part due to the fact that the Center's scientific staffing level is not optimal to meet the anticipated demands of the future, particularly the challenges presented by novel technologies. In 2007, the FDA Science Board's Subcommittee on Science and Technology reported that "CDRH does not have the personnel or resources in place to adequately support the science needs in the regulatory review process for the planned technologies of the future…."[46] CDRH's experts have a unique depth and breadth of knowledge about regulated products that serves them well, and the Center has undertaken efforts to increase its staffing levels in the past few years.[47] Nevertheless, there remain too few experts within each content area to adequately support the Center's mission-critical needs. There are some content areas, such as nephrology, plastic surgery, and infection control, for which the Center has only one clinical expert, and some content areas, such as immunology and oncology, where it does not have any clinical experts. Insufficient internal expertise can make it more difficult to make full use of currently available information, make fully informed and timely recommendations and decisions, and leverage external expertise. In the latter case, it is more challenging for CDRH to appropriately judge and make the best use of the input from an external expert with unique knowledge, particularly when it pertains to novel technologies, unless the Center has its own in-house expert in the same field. In addition to working to address the Center's scientific staffing needs in general, CDRH could enhance employee training and professional development to help current staff gain better working knowledge of fields with which they may otherwise be less familiar.

- 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 in Section 4.1.3, below.

[46] "FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology"(November 2007) at H-5. Available at http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_00_index.html.

[47] According to data from the Center's employee time reporting system, there was a net increase of roughly 9 percent in the total number of CDRH full-time equivalents (excluding field staff) from the end of FY 2005 to the end of FY 2009, due to increased funding from user fees and congressional appropriations.

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

CDRH's in-house knowledge has until recently been "siloed" in individual Offices. In the past few years, the Center has made a concerted effort to increase inter-Office integration and knowledge-sharing, in part through the Postmarket Transformation Initiative, the creation of the CDRH Matrix, and the development of "Total Product Life Cycle (TPLC) sheets," searchable electronic pages that bring together detailed pre- and postmarket information about specific device types from multiple databases.[48]

While these efforts have led to much progress, Center staff reported to the Task Force that there remain areas for improvement, including further efforts to integrate postmarket data into premarket processes. In particular, staff noted that it is difficult to determine where to seek advice about specific content areas, because it is difficult to identify who in the Center has appropriate expertise and experience to answer a given question.

As part of the Center's FY 2010 Strategic Priorities, additional work is underway to improve knowledge management across CDRH. The aim of this effort it to put in place personnel, systems, and processes that support the Center's mission-critical functions by making useful, meaningful scientific information about regulated products readily available to Center staff to meet their day-to-day needs.

- 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.

4.1.3. Finding: It is difficult for Center staff to tap meaningful external scientific expertise in a timely manner.

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

Given the need for additional expertise in certain areas to complement the Center's in-house expertise, and recognizing that it is unrealistic to maintain cutting-edge expertise and experience in-house, particularly with respect to novel technologies, current standards of care, the needs of device users and recipients, and the way users interact with specific devices in "real-world" practice, it is important for the Center to take advantage of the expertise of individuals outside the Center. Indeed, the 2007 FDA Science Board report stated, "It is recommended that new programs to engage outside scientific expertise in both review and research be initiated by CDRH."[49] Participants at the Task Force's public meeting also encouraged greater engagement between Center staff and outside experts.

The Center has taken steps since 2007 to increase its engagement with external scientific experts. This spring, for example, as part of the Center's FY 2010 Strategic Priorities, the CDRH External Expertise and

[48] A scaled-back version of the Center's Total Product Life Cycle database is available to the public on the CDRH Transparency Website at http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHTransparency/default.htm.

[49] "FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology" (November 2007), at H-15.

Partnerships (EEP) program published a manual for staff to use to more easily establish formal partnerships and agreements for research and collaboration with other organizations.[50] In addition, as mentioned above, the Center recently held a public workshop to establish the Medical Device Epidemiology Network (MDEpiNet), a consortium of academic institutions dedicated to advancing research and training in device epidemiology.[51] The Center hopes to collaborate further with this network and better leverage its extensive methodological expertise. These types of relationships can help the Center enhance its scientific knowledge, and develop a broad understanding of emerging scientific fields that can help guide regulatory decision making.

However, the Center's primary mechanisms for accessing external expertise regarding specific science-based regulatory decisions are the advisory panel process and other consultations with Special Government Employees (SGEs).[52] Statutory and regulatory requirements for convening an advisory panel, as well as logistical considerations, make it a relatively slow process, and, therefore, not suitable when the Center needs a fast response to scientific questions. In addition, while it is critical to assure that SGEs provide unbiased advice, the conflict-of-interest rules that currently exist for SGEs may be overly strict and can make it difficult to recruit and clear SGEs who have highly specific technical expertise that may be of particular value for a particular type of device. Center staff expressed a desire for less formal and less burdensome mechanisms for asking external experts specific scientific questions of interest, when such questions do not disclose proprietary information.

Center staff reported to the Task Force that informal interactions with industry as well as non-SGE academics and health care professionals are often a valuable source of scientific information. Interviewed staff indicated that field trips to visit manufacturers and "Vendor Days," in which manufacturers are invited to the Center to discuss their products, can be useful educational tools, provided that staff recognize potential biases in the information presented.

In addition, Center staff in some content areas have developed structures for routinely meeting with external experts to learn about emerging issues. Examples include the Orthopedic Device Forum and the Nanotechnology Working Group, which meet regularly and bring together experts from inside and outside FDA to exchange information and share individual expertise. Similarly, CDRH's Staff College runs a "Meet the Experts" program in neurology, which allows staff to engage with a range of external neurology experts on a regular basis. A few years ago, the Center's Defibrillator Working Group developed a process to retain and, to the extent legally permissible, regularly renew the employment of several SGEs, so that they could be "on call" to answer time-critical questions on postmarket issues. Each of these models takes time and effort to develop and sustain, however, and they have not been replicated for all content areas.

[50] EEP is comprised of three major programs that allow for structured engagement with external experts: the Medical Device Fellowship Program (MDFP); the Center's Partnerships and Technology Transfer operations; and the Critical Path Initiative. Additional information about EEP and its components is available at: http://www.fda.gov/AboutFDA/CentersOffices/CDRH/ucm188096.htm.

[51] *See* "Medical Device Epidemiology Network: Developing Partnership Between the Center for Devices and Radiological Health and Academia; Public Workshop."

[52] A Special Government Employees (SGE) is "an officer or employee … of any independent agency of the United States or of the District of Columbia, who is retained, designated, appointed, or employed to perform, with or without compensation, for not to exceed one hundred and thirty days during any period of three hundred and sixty-five consecutive days, temporary duties either on a full-time or intermittent basis." 18 USC §202. CDRH retains a cadre of SGEs with scientific expertise in various areas. SGEs typically interact with CDRH through the advisory panel process or through "SGE Homework Assignments," ad hoc consultations that do not entail a formal meeting.

- The Task Force recommends that CDRH, consistent with the Center's FY 2010 Strategic Priorities, develop a web-based network of external experts, using social media technology, in order to appropriately and efficiently leverage external expertise that can help Center staff better understand novel technologies, address scientific questions, and enhance the Center's scientific capabilities.

- The Task Force further recommends that CDRH assess best-practices for staff engagement with external experts and develop standard business processes for the appropriate use of external experts to assure consistency and address issues of potential bias. As part of this process, the Center should explore greater use of mechanisms, such as site visits, through which staff can meaningfully engage with and learn from experts in a variety of relevant areas, including clinical care. In addition to supporting interaction at the employee level, the Center should also work to establish enduring collaborative relationships with other science-led organizations.

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

When CDRH encounters new science, particularly evolving information about a product's risks and benefits, there is a wide range of actions that the Center might take in response. For example, given the details of a particular situation, it might be most appropriate to take a non-regulatory action, such as issuing a recommendation or other informative communication to the public. In other cases, new information that has come to light about a given device or device type might lead the Center to take a stronger action, such as modifying its premarket evidentiary requirements for future devices of the same type (*e.g.*, reclassification, special controls, requiring particular types of pre-clinical and/or clinical studies) in order to prevent similar problems from recurring.

Ideally, CDRH would be able to incorporate new scientific information into its decision making with little to no disruption to the Center's staff and external constituencies. In reality, however, no change is entirely seamless. There was a general consensus among Center staff and participants at the Task Force's public meeting that incorporating new and unexpected scientific information into the Center's decision making is not a process that can be automated or bound by strict prescriptive rules that would allow for perfect consistency. The heterogeneity of the products CDRH regulates, the multiple types of information that come to the Center, as well as their limitations, and the many other real-world variables that differentiate each particular case make it impossible to develop purely quantitative criteria or clearly delineated objective thresholds for taking a given course of action. Indeed, a key point of agreement for the participants at the Task Force's public meeting was that the Center ought to consider evolving scientific information on a case-by-case basis. In addition, change, no matter how predictable, is often disruptive.

Nevertheless, CDRH aims to provide as much predictability as feasible in its approach to new scientific information, and there are steps the Center should take to improve its current practice.

4.2.1. Finding: 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 expectations.

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.

Lack of predictability in regulatory decision making has been cited as the leading FDA-related concern for CDRH's regulated industry. This is especially important in the premarket arena, where uncertainty about CDRH's expectations can create significant additional costs for industry and hinder innovation.

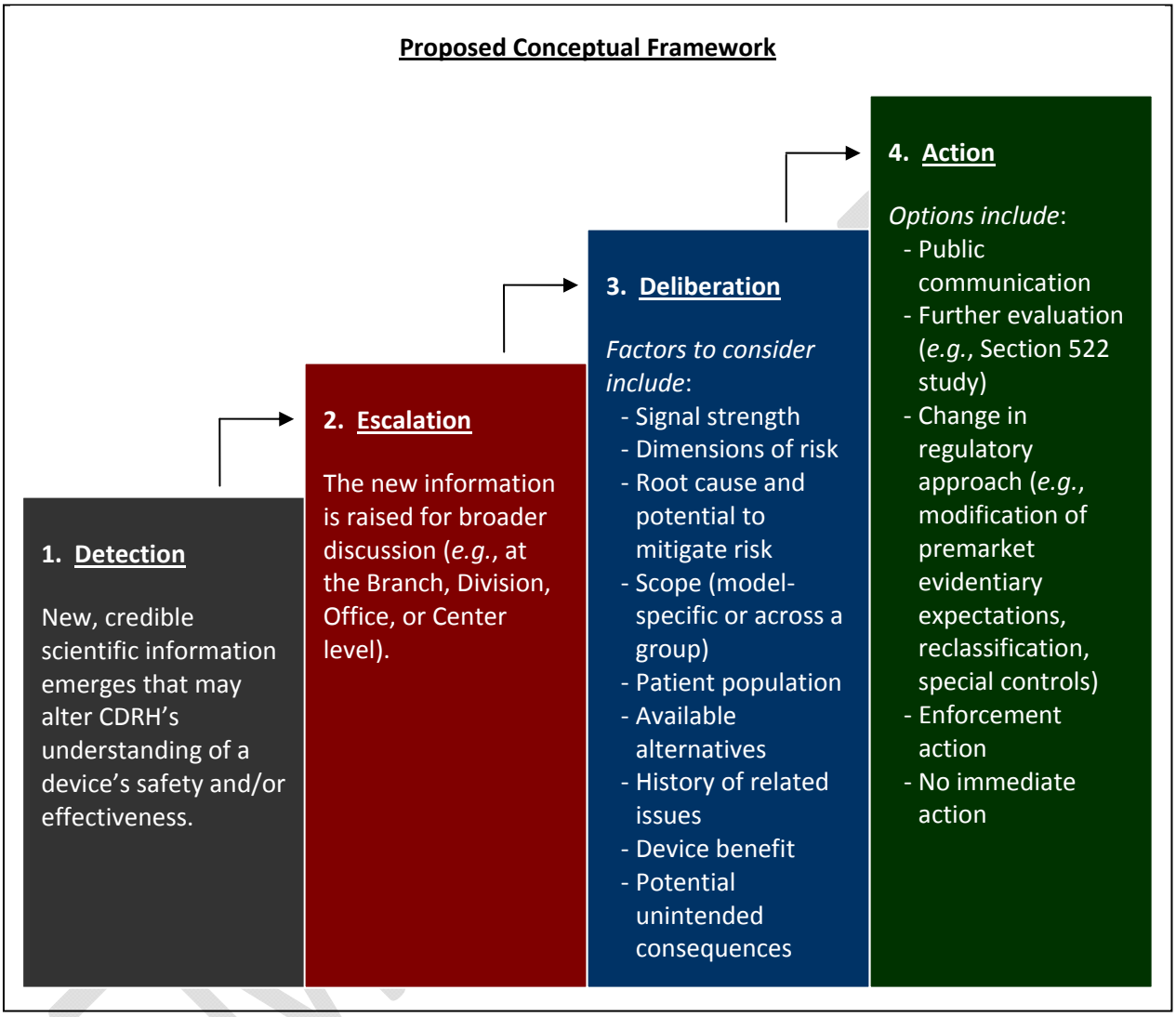
Increasing the predictability of CDRH's response to new scientific information depends in part on the Center taking a consistent and transparent approach toward that information. Currently, staff throughout the Center respond to new scientific information on a case-by-case basis. However, CDRH has not yet articulated a standardized, Center-wide approach to new information, particularly in the context of integrating postmarket information into the premarket review process.

With the development and adoption of the Total Product Life Cycle concept in the past few years, there has been a dramatic change in the culture of CDRH and an increased focus on integrating information from one part of a regulated product's life cycle into another. While there is agreement across the Center that such an approach is important for public health, it has been difficult to effectuate in a predictable manner. Some CDRH review staff, for example, reported to the Task Force that there is a lack of clarity about when a modification of premarket evidentiary expectations (*e.g.*, adding evidentiary requirements on the basis of a new concern, or eliminating pre-existing requirements as a technology becomes better understood) is justified on the basis of new postmarket information. Some review branches and divisions reportedly discuss on a regular basis their evidentiary expectations for the devices they review, in order to assure that reviewers' thinking is current and consistent. However, to date, CDRH has not articulated a process to be followed across *all* review divisions for evaluating new information and determining whether or not a change in evidentiary expectations (*e.g.*, requiring the use of a new type of assessment tool or study) is warranted on the basis of such information.

As a starting point for discussion and public comment, the Task Force has developed a broad conceptual framework for a business process CDRH could develop and implement for determining the appropriate response to new scientific information. The Task Force has also identified a few key principles that should be considered as this framework is put into practice. It is important to note that this framework focuses on developing a response to new information that may alter the Center's understanding of a device's safety and/or effectiveness. CDRH might also choose to adjust its regulatory approach to accommodate new scientific methods that support decision making; for example, under appropriate circumstances, it could issue guidance on using a new type of testing or analysis in support of premarket submissions. The Task Force decided to focus on evolving risk/benefit information in this and the following section of the report, because it represents the category of "new science" that the Center encounters most frequently. Such information may also warrant a rapid response, and, according to Center staff and external parties, it seems to be the source of greatest concern in terms of balancing adaptability and predictability.

The process would be comprised of four major steps, as depicted loosely in the box below: (1) detection of new scientific information; (2) escalation of that information for broader discussion with others; (3)

collaborative deliberation about how to respond, with a full consideration of the critical details of the situation at hand; and (4) action commensurate to the circumstance — including, potentially, deciding to take no immediate action.



Detection and Escalation. For the purposes of this conceptual framework, "detection" and "escalation" refer, respectively, to Center staff's recognition of new information that raises concerns about a regulated product's risks and/or benefits, and the elevation of that information for discussion with others in CDRH. Because some new information may have ramifications in multiple areas of the Center, it is critical to assure open internal communication and to develop a response collaboratively. Such an approach will also reduce the potential for inconsistency and duplication of effort that may be created if individual employees act in isolation. Depending on how broad the impact and implications of the new information are believed to be, escalation to different organizational levels (*e.g.*, Branch, Division, Office, or Center level) may be appropriate.

The Center is already working to create a mechanism for this kind of information-detection and sharing, with a primary focus on concerns that are raised about a specific device. CDRH is currently developing a Center-wide business process for "Signal Escalation," a systematic approach for cataloguing, elevating to

an appropriate level, and responding to detected "signals" — any information about a CDRH-regulated product that suggests an unexpected risk, an increased frequency of a known risk, or a shift in the risk/benefit balance associated with a product. Signals may take a variety of forms and come from a variety of sources across the Center, including, among other things, adverse event reports, published literature, mandated post-approval studies, FDA-sponsored research studies, and inspections. They may relate to safety and/or effectiveness, as information that calls either of these into question may alter the Center's understanding of a product's risks and benefits.

In practice, most signals reflect concerns about specific models of devices, and the current iteration of the Signal Escalation program is therefore tailored to accommodate model-specific signals. However, the basic framework of the program is flexible enough to accommodate clusters of signals that may reflect a broader concern about a group of devices — the kind of concern that might be more likely to result in the Center adjusting its premarket evidentiary requirements across the board for a device group, where permissible. As described further in the "Deliberation" section, below, one key factor to consider in determining an appropriate course of action is whether an identified issue is unique to a single device model or may affect an entire device group.

Under the Signal Escalation model, individual employees enter signals into a web-based system for tracking and sharing with others in the Center. Employees are expected to work with their first-line managers to determine when it is appropriate to "escalate" a signal for broader discussion with others, and what level of escalation is warranted.

At present, the Signal Escalation process is still in development and, as discussed above, is focused primarily on addressing model-specific concerns. Finalization, implementation, and staff training are expected to be completed this year, as part of the Center's FY 2010 Strategic Priorities. An expansion of the program, in conjunction with the development of a more robust knowledge management infrastructure with the capacity to pool information from a large number of signals or other forms of information over time, will be necessary to better support the identification of concerns that affect an entire group of devices. CDRH's understanding of products' risks and benefits improves with experience, and any new information that raises concern must be considered within the full context of the Center's current knowledge.

Deliberation. Once new information is raised for discussion, several critical factors should be considered in order to determine what action is appropriate in a given case. These include the factors listed in the table below, many of which were raised by participants at the Task Force's public meeting.

Factor	Relevant Questions
Signal Strength	• What degree of confidence is there that the new information is valid and accurate? What is the quality of the data and/or data source? • Is the new information supported by multiple signals? By multiple data sources?
Dimensions of Risk	• Is the information related to device safety, effectiveness, or both? • What is the severity and likelihood of device failure or malfunction (if relevant)? • What is the severity and likelihood of risk to patients?

Factor	Relevant Questions
Root Cause and Potential to Mitigate Risk	• If the root cause has not yet been identified, what can be done to identify it? • What kinds of actions could mitigate the identified root cause(s)? For example, could a problem be mitigated through improvements in device design? Through standardized labeling (*e.g.*, warnings or instructions)? Through standardized training programs? Is a problem due to industry practice that can be corrected through education or enforcement actions? • What kinds of actions could mitigate risk to patients, even if they do not address the root cause(s) *per se* (*e.g.*, in cases where the root cause is unknown or cannot readily be mitigated)?
Scope	• Are the identified problem(s) and its root cause(s) unique to a specific device model, or might they affect other devices in the same group? • Is the risk related to on- or off-label use? If off-label, can the use be well-characterized?
Patient Population	• Can the exposed patient population be characterized? • Are there any special considerations about the patient population (*e.g.*, widespread vs. limited use, specific vulnerabilities)?
Available Alternatives	• Are other medical products or diagnostic/therapeutic options readily available? If so, how do they compare to the device in question in terms of safety and effectiveness?
History of Related Issues	• Is the new information part of a larger pattern of issues (*e.g.*, with respect to a given manufacturer or group of devices)?
Device Benefit	• What is the benefit of the device in the intended patient population? • Would any of the proposed actions negatively impact the degree or likelihood of benefit to patients?
Potential Unintended Consequences	• Should any other special considerations be taken into account with respect to a particular course of action (*e.g.*, departure from or creation of a new precedent, public perception, potential for a shortage)?

Action. As described previously, there are a number of actions CDRH could take in response to new scientific information, taking into consideration the key factors listed above.

There may be situations, for example, in which public communication alone would be an appropriate response to new scientific information. The content, intended audience, and mechanism for such communication might be influenced by the circumstance at hand. For example, there may be a situation where outreach is targeted toward a specific patient or practitioner population.

Ordering a Section 522 study could be appropriate in situations where further information is needed to understand the extent of the public health issue. Where it is suspected that similar problems may be occurring across a device group but further information is needed, it may be appropriate to order 522 studies for all marketed devices in that group, and to initiate the same type of study for devices in the same group that are currently under development or review, once they enter the marketplace.[53]

The Center might consider modifying its premarket requirements, where permissible, in situations where a root cause of an identified problem is likely to be shared across a device group, and where that root cause could be addressed or mitigated by a specific improvement in device design, testing, labeling, or training. When CDRH does modify its premarket evidentiary requirements, it would use a risk-based approach to determine whether the new requirements should also apply to devices currently under review and/or to devices currently on the market.

The Center would generally take an enforcement action if the new scientific information pointed to a violative action on the part of a single manufacturer, or where the manufacturer fails to take adequate corrective action on its own initiative. Systematic weaknesses across an industry may result in the Center's engaging in targeted industry education and outreach activities.

There might also be situations in which new scientific information is raised and, after consideration, no immediate action is determined to be warranted.

Implementation of the Conceptual Framework. In putting this approach into practice, the Center should consider several key principles.

First, the process should allow for a range of individuals to participate in the deliberation phase, including managers and employees. As mentioned previously, collaborative deliberation would help take into consideration potentially cross-cutting issues that could have ramifications in other areas, and it would help assure consistency among employees who work with the same types of devices. In the interest of providing such consistency, decisions to change regulatory expectations should be made by managers.

To support this principle, CDRH should establish a Center Science Council, under the direction of the Deputy Center Director for Science. This group should be comprised of experienced employees and managers, including but not limited to the team of clinical trial experts described in Section 4.1.1.1 of this report. Consistent with the President's memorandum on scientific integrity,[54] the Science Council should be responsible for providing Center-wide oversight in a range of scientific areas. As part of its work, the Science Council should meet regularly and be available, as needed, to discuss and vet potential changes in the Center's regulatory expectations on which staff at lower organizational levels wish to seek additional advice from a wider range of experts, or whose impact could be cross-cutting enough to warrant broad or Center-level attention. Another role for the Science Council relates to

[53] In October 2009, for example, CDRH ordered all manufacturers of dynamic stabilization systems already on the market to conduct Section 522 studies to collect clinical data on a number of potential safety issues. At the same time, the Center requested that manufacturers of new dynamic stabilization systems or components to submit clinical information during premarket review. For more information, *see* "FDA News Release: FDA Orders Postmarket Surveillance Studies on Certain Spinal Systems" (October 5, 2009). Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm185312.htm.

[54] Obama B, Memorandum for the Heads of Executive Departments and Agencies (March 9, 2009). Available at: http://www.whitehouse.gov/the_press_office/memorandum-for-the-heads-of-executive-departments-and-agencies-3-9-09/.

increasing the consistency of 510(k) decision making, as described in greater detail in the preliminary report of the 510(k) Working Group.

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 mechanism and basis for prioritization need to be further considered.

- The Task Force recommends that CDRH develop and implement a business process for responding to new scientific information in alignment with the framework and principles discussed above. The Center should also develop metrics to determine whether or not the new process is effective.

The implementation of and adherence to the process described above could significantly help the Center achieve more predictable outcomes as to when it decides to change its regulatory expectations. In addition, and over time, as better data sources and analytic methods are developed, CDRH could strengthen these processes with the use of evidence synthesis and quantitative decision making, when appropriate. Evidence synthesis and quantitative decision making could be additional tools for the Center to use to increase consistency in the decision making process by providing a robust, reproducible, and data-driven framework for making decisions. However, given CDRH's current data sources, methods, and capabilities, evidence synthesis and quantitative decision making are desirable but far from readily attainable objectives. In addition, because evidence synthesis and quantitative decision making are resource-intensive and time-consuming, their near-term use may be limited. In the longer term, with more experience, their use may be integrated into Center processes on a broader scale, as practical.

- 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.

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

The final critical element of incorporating new science into CDRH's decision making is clear and timely communication to the Center's staff and external constituencies about its actions. CDRH staff and several members of the public emphasized the importance of early communication with all parties that might be affected by a Center action, and transparency about the Center's decision making process and rationale.

4.3.1. Finding: As CDRH incorporates new science into its decision making, it is difficult for the Center to communicate its current or evolving regulatory thinking to all affected parties in a timely and meaningful manner.

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

The Center has taken steps over the past few years to increase its use of tools that allow for early and

broad sharing of information about emergent public health issues to its external constituencies. However, existing processes for communicating the Center's current regulatory thinking have not been nimble enough to reflect rapidly changing science.

In particular, staff throughout CDRH and members of the public have expressed frustration with the length of time it takes for the Center to develop guidance. Regulatory changes, including reclassification and establishment of special controls, are also time-intensive. As a result, it can be difficult for the Center to rapidly provide formal communications regarding changes in regulatory expectations that may occur on the basis of new scientific information.

As part of the Center's FY 2010 Strategic Priorities, CDRH is working to improve guidance and regulation development. In addition, the Center has, in certain cases, sent letters to all manufacturers of a particular type of device about which it has concerns and for which it is changing its premarket evidentiary expectations, in advance of initiating procedures to formalize the change through new or modified device-specific guidance. This year, such letters have been sent to manufacturers of radiation therapy devices,[55] negative pressure wound therapy devices,[56] and infusion pumps.[57] In these letters, some of which have been made available to the public on the Center's website, CDRH has communicated its concerns and their bases, in order to provide all affected manufacturers with early notice of its intentions. The letters have not been intended to serve as a substitute for guidance, and they have not defined CDRH's current expectations for the identified device types. Rather, they have encouraged the manufacturers in question to meet with Center staff if they plan to modify or develop a new device of the same type, so that they can be advised of the Center's expectations.

At the internal town hall that the Task Force and the 510(k) Working Group co-hosted on February 24, 2010, a staff member pointed to the long-standing practice of the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) of posting online FDA reviewers' summaries for all cleared submissions. By explaining each decision and its basis, these summaries provide manufacturers with regularly updated information about reviewers' expectations. To date, the Office of Device Evaluation has not adopted this approach. This issue is discussed in greater detail in the preliminary report of the 510(k) Working Group.

- 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.

- The Task Force further recommends that CDRH establish as a standard practice sending open "Notice to Industry" letters to all manufacturers of a particular group of devices for which the

[55] "Letter to Manufacturers of Linear Accelerators, Radiation Therapy Treatment Planning Systems, and Ancillary Devices" (April 8, 2010). Available at http://www.fda.gov/Radiation-EmittingProducts/NewsEventsRadiationEmittingProducts/ucm207835.htm.

[56] *See* "Medical Device Home Use Initiative" (April 2010) at 8. Available at http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/HomeUseDevices/UCM209056.pdf.

[57] "Letter to Infusion Pump Manufacturers" (April 23, 2010). Available at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/InfusionPumps/ucm206000.htm.

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.[58] 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.

In addition to communicating in a clear and timely manner to industry, it is important for the Center to convey its current understanding of the risks and benefits of devices to patients and practitioners. As described above, the Center has taken steps in recent years to improve risk communication and outreach to the public, including the development of tools to support earlier communication. Another important vehicle for medical device risk/benefit information is product labeling. However, medical device labeling is not always written in a clear, user-friendly manner, and it is not always readily available to patients. The Center recently announced a pilot program to develop an online repository of labeling for home use medical devices.[59]

- 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.

[58] Under FDA's Good Guidance Practices regulation and consistent with section 701(h)(1)(C) of the FDCA (21 USC §371(h)(1)(C)), Level 1 guidance documents may be implemented without FDA seeking prior comment if the agency determines that prior public participation is not feasible or appropriate, such as when immediate implementation is necessary to protect the public health. 21 CFR 10.115(g)(2). FDA will invite comments at the time of issuance of such guidance, and if the agency receives comments, it will review those comments and revise the guidance when appropriate. 21 CFR 10.115(g)(3).

[59] *See* "Agency Information Collection Activities; Proposed Collection; Comment Request; Invitation to Manufacturers and Distributors to Voluntarily Submit Final Product Labeling and Information Electronically for all Devices Cleared by the Food and Drug Administration for Home Use; Notice of Pilot Program," 75 Fed. Reg. 95 (May 18, 2010), pp. 27791-17793. Available at http://edocket.access.gpo.gov/2010/pdf/2010-11810.pdf.

4.3.2. Finding: There has been a lack of transparency about the Center's rationale for taking a particular course of action in response to new science.

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.

Center staff and industry representatives have reported that when CDRH decides to take an action, such as changing its premarket evidentiary expectations, on the basis of new scientific information, the rationale for that action is not always adequately explained. Manufacturers have noted that review staff sometimes request additional information that does not immediately appear relevant or necessary. On the other hand, interviewed staff noted that, at times, the basis for a given request may be an important scientific lesson learned from experience with other, similar products. In such cases, reviewers and managers may be reluctant to explain the rationale for the request because of concerns about confidentiality. Staff reported that in these cases, it can be challenging to readily convince manufacturers to comply with requests for additional information, even when those requests are justified from a scientific and regulatory perspective.

- 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.

- The Task Force further 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,[60] consistent with the Center's FY 2010 Strategic Priorities and the work of the FDA Transparency Task Force.[61] 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, as discussed above) 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.

[60] *See* "CDRH Transparency." Available at http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHTransparency/default.htm.

[61] *See* "FDA Transparency Task Force." Available at http://www.fda.gov/AboutFDA/WhatWeDo/FDATransparencyTaskForce/default.htm.

5. CONCLUSION

To protect and promote the public health, the Center for Devices and Radiological Health must have the staff, tools, infrastructure, and processes in place to adapt to new science through an approach that is predictable, risk/benefit-based, and well-communicated. Each of the Task Force's recommendations represents an area of significant opportunity for CDRH to improve its effectiveness in fulfilling its two-part mission.

As the Task Force works with other Center staff, after the receipt and review of public comments, to develop an implementation plan for its recommendations, it will also determine an appropriate mechanism and timeframes to evaluate the impact of these actions, and make adjustments as necessary.

APPENDIX A: CHARGE FROM THE CENTER DIRECTOR

FDA's Center for Devices and Radiological Health (CDRH) uses science to guide premarket approval and clearance decisions, as well as postmarket oversight and compliance actions.

CDRH seeks to provide industry with predictable regulatory pathways that foster innovation. At the same time, the Center's regulatory decision making process must be able to adapt as science evolves and as new information emerges about the risks or benefits of a given device, in order to successfully fulfill our mission to protect and promote the public health.

Task Force on the Utilization of Science in Regulatory Decision Making

CDRH is forming an internal Task Force on the Utilization of Science in Regulatory Decision Making to review how CDRH uses science in the regulatory decision making process, and to make recommendations on how the Center can quickly incorporate new science into this process while providing manufacturers with predictable pathways to foster innovation. *New science* refers to new data about the risk/benefit profile of devices; new information about manufacturing practices and processes; new scientific fields and technologies, such as nanotechnology; and new regulatory science, including analytic, tools.

The Task Force will seek input from Center staff and external stakeholders to address the following questions and make recommendations:

- How is new science currently used to inform Center premarket approval or clearance decisions? What challenges does this present for providing reasonable assurance that devices are safe and effective while providing manufacturers with predictable pathways that foster innovation?
- How should new science be used to inform and support Center premarket approval or clearance decisions? Specifically:
  - What should be the threshold for using new science to establish new or modify current evidentiary standards for approval or clearance?
  - How should CDRH determine and set as Center policy new or modified evidentiary standards so as to enhance predictability and foster innovation?
  - How should CDRH communicate new or modified evidentiary standards to industry and other stakeholders?
  - How should CDRH use new or modified evidentiary standards for devices under development? For device submissions already under review? For devices already on the market?
- What proactive steps should CDRH take to address gaps in scientific knowledge and reduce uncertainty in science-based regulatory decision making?

The Task Force will submit a draft written report to the Center Director approximately five months after the group is convened and a final written report six months after the group is convened.

APPENDIX B: SUMMARY OF STAFF FEEDBACK

Shortly after the Task Force on the Utilization of Science in Regulatory Decision Making was convened, members of the Task Force met with several CDRH staff focus groups to ask a series of questions about how the Center can and should respond to new and evolving science. The groups were selected to represent a range of perspectives within the Center, spanning multiple Offices, organizational levels, and scientific content areas.

The following groups were interviewed:

- Cardiovascular Standards Specialty Task Group (STG)[62]
- Human Factors Working Group
- Interagency Oncology Task Force
- Materials STG
- Selected Reviewers from the Office of Device Evaluation
- Selected Reviewers from the Office of In Vitro Diagnostics
- Nanotechnology Reviewer Network
- Radiology STG and Medical Imaging Experts
- Software/Informatics STG and Software Groups from the Office of Device Evaluation and the Office of Science and Engineering Laboratories
- Sterilization STG
- Tissue Engineering STG and Tissue Engineering Working Group

A number of themes emerged from these conversations about both the practices that had proven useful in understanding and using emerging science in regulatory determinations, and actions as well as obstacles to obtaining the most current information and the best scientific expertise.

The Task Force also presented the case studies and questions from its public meeting[63] to CDRH staff for comment on an Internet-based social media platform called Traction, which is open to all staff, and at a Center-wide internal town hall meeting held on February 24, 2010.

This Appendix presents a summary of these discussions and comments.

A. Adapting to New Scientific Information

New Scientific Information. CDRH staff members discussed challenges they currently face in evaluating whether new scientific information merits changes to premarket review requirements. Reviewers and other staff members expressed frustration that principles favoring the "least burdensome" means of regulation interfered with the ability of reviewers to adapt regulatory approaches to new scientific information. Reviewers also noted that previous review decisions were sometimes treated as precedent-setting, interfering with their ability to respond appropriately to new information about products under review because of concerns about creating an uneven playing field.

[62] Standards Specialty Task Groups (STGs) are content-specific staff working groups that meet periodically to discuss the development of consensus standards as part of the CDRH Standards Program. STGs exist for a variety of content areas and are comprised of representatives from across the Center.

[63] A summary of the Task Force's public meeting can be found in Appendix C.

Others pointed out the need for better data sources (*e.g.*, registries) and better methods (*e.g.*, simulations, modeling) to adequately assess a product's risks and benefits. In addition, there were points made about the need to better integrate postmarket data into premarket review and decision-making processes.

The Need for Transparency. Staff members reported problems with the pace of current guidance development practices, stating that changes in science and corresponding needs for changes to guidance outpace the guidance development process.

Staff comments acknowledged a role for additional education to industry about the 510(k) program in particular, and suggested the creation of idealized mock 510(k) applications to provide instruction and solicit comment from regulated industry.

One staff comment suggested the use of technology or device-specific "wiki" sites to gain consensus about changes to regulatory expectations from industry, academia, public societies, and CDRH staff. The same comment advocated an enhanced role for the CDRH Ombudsman complemented by a group of FDA staff dedicated to outreach activities to communicate such basic information as the organizational structure of FDA and the role of scientific reviewers.

B. Adapting to Novel Technologies or Novel Uses of Existing Technologies

Premarket Review of Novel Technologies. Some discussants from the staff focus groups stated that having samples of novel devices submitted with premarket applications would be valuable.

Other discussants noted challenges related to inflexible premarket review timeframes, with insufficient time allowed for review of complex systems.

C. Enhancing CDRH's Technical Competency and Analytical Capability

Means of Improving Expertise. Discussions with staff focus groups revealed that regulatory site training has occurred in some instances. CDRH staff who had participated in onsite introduction to new technologies acknowledged the value of the experience but presented concerns about the potential pitfalls on relying on interested parties for information about new technologies. Two staff comments suggested that CDRH proactively engage technology transfer and incubator groups by sending Center experts for onsite training.

CDRH staff noted that expertise exists in several areas within the Center, but better means of communicating the expertise, such as enhanced use of internal networks and Traction, are needed. A theme that came up repeatedly during discussions with staff focus groups was that while advisory panels can be enormously helpful in addressing specific scientific questions, the process is cumbersome and the most highly-qualified experts are commonly conflicted.

APPENDIX C: SUMMARY OF FEBRUARY 9, 2010 PUBLIC MEETING

In its Federal Register notice of December 18, 2009, CDRH announced a public meeting entitled "Incorporation of New Science Into Regulatory Decisionmaking [*sic*] Within the Center for Devices and Radiological Health," which was held on February 9, 2010.[64] The purpose of this meeting was to hear the perspectives of various external constituencies on strategies and means for incorporating new science into CDRH's regulatory decision making.

As described in the notice, the meeting consisted of a moderated discussion between CDRH staff and invited experts from the private and public sectors about several specific questions related to the Center's response to new science. The Task Force selected the discussants with the aim of allowing for a range of different viewpoints to be represented. The discussants were not asked to develop consensus recommendations, but rather to provide their individual perspectives. The topics for discussion were presented in conjunction with four hypothetical case studies for consideration. There was also an opportunity for general attendees to provide feedback on the discussion topics during two open sessions.[65]

This Appendix presents the four case studies that served as a basis for discussion, as well as a summary of the related comments raised at the meeting. Relevant questions from the Federal Register notice are indicated below each case study as Questions of Interest.

Case Study 1: Postmarket Information

Scenario A. CDRH clears Device X for marketing through the 510(k) process. Device X is cleared for a specific intended use. Several years later, a pattern of Medical Device Reports (MDRs) that have been submitted to CDRH calls into question the safety of the device when used in the long term for its cleared use. A number of other devices of the same type and with the same intended use as Device X are on the market when this new safety information comes to light. There is also a device of the same type, Device Y, under review through the 510(k) process. The 510(k) submission for Device Y cites Device X as a predicate.

Scenario B. CDRH approves Device Z for marketing through the PMA process on the basis of favorable results in a pivotal clinical trial. Several years later, a compelling peer-reviewed publication reports that an attempt to replicate these clinical trial results was unsuccessful. A number of other devices of the same type and with the same intended use as Device Z are PMA-approved and on the market when this article comes to light. There is also a device of the same type and for the same intended use, Device Q, under review through the PMA process.

Questions of Interest:

- When CDRH gains new scientific information about a particular product or type of product, what should the criteria be for changing CDRH's expectations of the evidence necessary for

[64] "Incorporation of New Science Into Regulatory Decisionmaking [*sic*] Within the Center for Devices and Radiological Health; Public Meeting; Request for Comments," 74 Fed. Reg. 242 (Dec. 18, 2009), pp. 67237-67238. Available at http://edocket.access.gpo.gov/2009/E9-30114.htm.

[65] The meeting agenda, a list of the invited discussants, an audio recording, and a verbatim transcript, are available at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm191579.htm.

pre- or postmarket regulatory decisions, keeping in mind our mission to protect and promote the public health, as well as our statutory and regulatory framework?
- When such changes are warranted, how should CDRH apply them to devices currently under review?
- When such changes are warranted, how should CDRH apply them to products currently on the market?

One focus of the discussion related to the Center's use of MDRs. Some discussants pointed to the limitations of MDRs, including that they typically contain incomplete information. Some discussants recommended that CDRH consider MDR information in the context of potentially more robust data from clinical trials and/or controlled studies of engineering that may have been conducted to support premarket clearance or approval. Several discussants recommended that CDRH consider MDR information in the context of information on the scope of use (including so-called "denominator data," *i.e.*, the total number of units of a device used, as well as the number used in populations of interest), the environment(s) of use (*i.e.*, a clinical setting or the home), and the "learning curve" associated with new or unfamiliar devices.

Discussants encouraged CDRH to turn to manufacturers to obtain information about root cause(s) and trends, and to complement MDR data with information from other sources.

A key message voiced by the discussants was to fully consider the risks and benefits of a product. If a product's risk/benefit profile were to change meaningfully (though the discussants were unable to define "meaningful"), then it would be appropriate for CDRH to take action. This point seemed to resonate with all parties.

Case Study 2: Changes in Clinical Science

A company works with CDRH to design a three-year clinical trial to study an investigational device, Device J. The trial will assess the effect of Device J on a particular measurable variable, which is meant to be a surrogate for a specific clinical outcome. In year two of the trial, CDRH learns from other compelling peer-reviewed studies in publication that the surrogate does not reliably track the expected clinical outcome.

Consider the following variations on the case above:

- ***Scenario A.*** Prior to this point, CDRH has not cleared or approved any other devices on the basis of clinical trials using this surrogate endpoint.
- ***Scenario B.*** Prior to this point, CDRH has cleared or approved a number of other devices on the basis of clinical trials using this surrogate endpoint.
- ***Scenario C.*** At this point, there are several other investigational devices that are being tested in clinical trials using this surrogate endpoint.
- ***Scenario D.*** At this point, CDRH is reviewing a PMA for an investigational device that was tested in a clinical trial using this surrogate endpoint.

Questions of Interest:

- When CDRH gains new scientific information about a particular product or type of product, what should the criteria be for changing CDRH's expectations of the evidence necessary for pre- or postmarket regulatory decisions, keeping in mind our mission to protect and

promote the public health, as well as our statutory and regulatory framework?

- When such changes are warranted, how should the Center communicate them to industry, consumers, and other external constituencies? Should CDRH have a new regulatory paradigm for communicating with outside parties?
- When such changes are warranted, how should CDRH apply them to devices currently under review?

The discussants made the point that a manufacturer has the onus to show that a trial endpoint is relevant and/or meaningful. If a trial endpoint were not shown previously to be meaningful, then it should not be assumed that it would be acceptable for use in a pivotal trial. The discussion did not include objection to a trial commencing with a previously unvalidated endpoint, if the case could be made that there would be reasonable knowledge gained, there were no better alternatives, and the subjects were sufficiently protected. The Center could then consider this essentially to be a feasibility study.

The discussants acknowledged that when clinical trials were difficult to perform based on scientific or logistical issues, the Center would be expected to make assessments and decisions on the basis of the available data and in as predictable and consistent a manner as practical. In addition, the Center was urged to draw on outside expertise and communicate significant changes in its expectations broadly and as early as possible.

The discussion included the opinion that all parties should understand that from scientific, statistical, and regulatory perspectives, uncertainty is unavoidable at the time the Center makes clearance/approval decisions. It is not possible to address all questions in the premarket evaluation, and the regulations/statutes do not allow the Center to ask for such information. In light of these considerations, discussants posed the idea of a pathway for limited approval/clearance, with the suggestion of a pathway parallel to CMS' "coverage with evidence development" option.

Case Study 3: Technological Improvements

CDRH clears Device W through the 510(k) process. At the time of clearance, it is considered to be state of the art. A number of other devices of the same type and with the same intended use as Device W soon come onto the market. Over the following years, devices of the same type and for the same intended use evolve through several generations, leading to a new state of the art device with a significantly more favorable risk-benefit profile than that of Device W and similar older devices. Device W and similar older devices are still in market use. There is also a device of the same type, Device R, under review through the 510(k) process. Device R has a similar risk-benefit profile to that of Device W, and the 510(k) submission for Device R cites Device W as a predicate.

For the purposes of discussion, assume that all of the later-generation devices use Device W as their predicate.

Consider the following variations on the case above:

- ***Scenario A.*** The newest devices are shown to be safer than Device W and similar older devices, but seem to have roughly the same level of effectiveness.
- ***Scenario B.*** The newest devices are shown to be more effective than Device W and similar older devices for their intended use, but seem to have roughly the same level of safety.
- ***Scenario C.*** The newest devices are shown to be both safer and more effective than Device

W and similar older devices.

Questions of Interest:

- When CDRH gains new scientific information about a particular product or type of product, what should the criteria be for changing CDRH's expectations of the evidence necessary for pre- or postmarket regulatory decisions, keeping in mind our mission to protect and promote the public health, as well as our statutory and regulatory framework?
- When such changes are warranted, how should CDRH apply them to devices currently under review?
- When such changes are warranted, how should CDRH apply them to products currently on the market? For example, how should CDRH treat "first-generation" products as new and improved versions are developed?

In discussing incremental improvements in a medical device, the discussants generally agreed that it would be difficult to define the point at which such evolution results in a meaningful difference from prior versions of the device. Discussants also stated that life-sustaining devices should be assessed differently than those used for less critical needs, and pointed out the potential harm of limiting or denying access to older devices that may fill a critical need. Many discussants suggested that market forces are sufficient to drive device improvement, and that no regulatory intervention is needed to remove "outmoded" products from the marketplace.

As in the earlier case study discussions, the discussants returned to the question of what specific criteria might need to be met to warrant Center action. The discussants reaffirmed that it would be difficult to define such criteria. As part of this discussion, the Center was again recommended to consider "denominator data" to understand better the significance and scope of reported adverse events.

The discussants again focused on communication, and recommended that CDRH communicate its scientific understanding and expectations early (as close to real-time as practical), even, at times, when there is less than complete certainty about new information.

While some discussants suggested that it may be helpful to include "device genealogy," *i.e.*, a discussion of predicate devices and any incremental modifications, within product labeling, others questioned the utility of such an approach.

Case Study 4: Novel Technology

A device currently under review within CDRH is a first of a kind device that uses a new material with unique or unknown biocompatibility properties.

Questions of Interest:

- Assessing the safety and effectiveness of a novel technology can be challenging because the extent of information on and the level of understanding of the technology's risk-benefit profile or manufacturing process is less mature than that of a technology for which there is extensive "real-world" experience. What steps should CDRH take to assure that novel technologies or novel uses of existing technologies are safe and effective, without creating barriers to innovation, keeping in mind our statutory and regulatory framework?

- With current resources, what proactive steps should CDRH take to address gaps in staff members' knowledge about new science and reduce uncertainty in science-based regulatory decision making?

The discussants suggested that a reasonable approach would rest upon the principles of risk-based decision making. In this approach, new materials would be more readily acceptable when there were greater limitations in patient exposure, *i.e.*, devices involving non-contact materials, shorter-term exposure, or single-use would be considered lower-risk than implanted devices. Discussants cautioned CDRH to consider potential risks in the context of potential benefits, and not in isolation.

APPENDIX D: SUMMARY OF WRITTEN PUBLIC COMMENTS

In its Federal Register notice of December 18, 2009,[66] CDRH solicited comment on how the Center should respond to three broadly defined challenges presented by new science and on several case studies intended to illustrate these challenges. The public docket was open from December 18, 2009 through February 24, 2010.

A total of 16 comments were submitted to the docket, including comments from organizations of health care professionals, other nonprofit organizations, trade groups, device manufacturers, and regulatory affairs professionals.

This Appendix presents a summary of these comments.

A. Adapting to New Scientific Information

New Scientific Information. Several comments stated that the definition of "new scientific information" was unclear. These comments sought clarity on the level of evidence necessary for CDRH to take regulatory action. One comment noted that CDRH seemed to treat both Medical Device Reports (MDRs) of new adverse events and "compelling peer-reviewed studies" as potential sources of new scientific information; according to another comment, the public notice gives the impression that "anecdotal [or] observational" information could qualify as new scientific information. All three of the trade organizations that commented and several members of industry cautioned against reliance on MDRs as a sole basis for changes to a regulatory approach.

One comment stated that although MDRs, recalls, and scientific literature could be sufficient scientific grounds to trigger changes to CDRH's regulatory decision making, these sources of information should first be substantiated by valid scientific information. Similarly, another comment stated that CDRH should consider changes to premarket and postmarket regulatory requirements only when justified by valid scientific evidence, but suggested that the level of evidence necessary to justify regulatory action could be different depending on whether the new information related to the safety or effectiveness. A related comment was that "additional studies" may be necessary before taking regulatory action based on new scientific information related to a device's effectiveness. Another comment suggested that, to justify regulatory action, new scientific information should be "clear and convincing." The comment did not elaborate on when new scientific information reaches the threshold of "clear and convincing."

Responding to the first case study, comments compared thresholds for regulatory action pre- and postmarket, and approaches for responding to information that affects a single device compared to information that affects multiple devices. Comments stated that a peer-reviewed study should not suffice to remove a device from the marketplace because the quality of the data and statistical validity is likely to be lower than for the pivotal trial submitted to obtain marketing authorization. Similarly, one comment stated that devices under review should not be held to a higher standard than cleared devices are, even when new information may have led to a different premarket decision had it been available during premarket evaluation of the marketed devices. One trade organization suggested that potentially affected PMA holders should have an opportunity to critique the peer-reviewed study before

[66] "Incorporation of New Science Into Regulatory Decisionmaking [*sic*] Within the Center for Devices and Radiological Health; Public Meeting; Request for Comments," 74 Fed. Reg. 242 (Dec. 18, 2009), pp. 67237-67238. Available at http://edocket.access.gpo.gov/2009/E9-30114.htm.

CDRH takes any action based on peer-reviewed literature. This same group suggested that new information may change the data requirements for future PMAs if the new information is compelling and shows problems with study design or other data issues, but if the information does not affect safety and effectiveness, no action against marketed devices should be taken.

Concerning the use of surrogate endpoints, the same trade organization suggested that if more than one peer-reviewed study confirmed problems with data used to support a device marketing application an advisory panel should be convened to consider the validity of the endpoint. This comment was echoed by industry comments, which stated that if the surrogate endpoint is found to be invalid, FDA should work with the manufacturer to devise an alternative endpoint and that "every effort" should be taken to preserve the results of the clinical study.

Risk-Based Decision Making. Another theme that emerged from several comments was the importance of factoring risk and benefit into any regulatory response to new scientific information. One comment stated that although MDR reports may highlight safety issues that require an expeditious response, the Center should perform a risk/benefit analysis before responding to such reports. Many comments noted that FDA's current decision-making processes account for both the risks presented by a device in light of new information and the benefit of the device. These comments believed any approach adopted by the Center to new scientific information should retain a risk-based focus and that the Center should affirm its commitment to using risk/benefit analyses in responding to new scientific information. A trade organization recommended that FDA also consider the risk presented by non-use of the device. One comment from industry who advocated a risk/benefit approach to responding to new scientific information also stated that regulatory changes based on new scientific information should be implemented in a manner consistent with the least burdensome means of regulation.

The Need for Transparency. The need for transparency as the Center assesses and develops an approach to new scientific information was another common theme among the written public comments. For the most part, comments advocated increased use of existing public processes and, with the exceptions discussed below, did not suggest new processes or significant changes to existing processes to improve communication with industry or other sectors of the public. Some comments cautioned, however, that while communication of new information with provider organizations is essential, the Center should carefully consider sharing information about particular devices or device classes with the public. A trade organization believed that in some circumstances, confidentiality concerns should trump perceived needs for regulatory change, urging CDRH not to create new or changed obligations based on information that could not be shared with the affected manufacturers.

Several comments suggested that a variety of existing processes might be appropriate mechanisms for communicating changes in CDRH's evidentiary expectations, including public hearings and meetings, advisory panel meetings, guidance development, and rulemaking. One comment suggested that any process for communicating changes to regulatory expectations based on new information should include: (1) early access to the new information to affected manufacturers; (2) informal and formal dialogue between FDA and affected manufacturers; and (3) written guidance on the regulatory effect of the new information on manufacturers. Several members of industry advocated an ongoing dialogue consisting of meetings with "key industry leaders," without specifying whether other members of the public should be invited to these meetings.

The topic of guidance documents came up in several comments. Some comments expressed a preference for having changes communicated by new or revised guidance documents made available to

industry as early and quickly as possible. One comment, however, acknowledged problems in CDRH's current guidance development processes, noting that new guidance documents proposed by CDRH had not been issued and that CDRH management should address the backlog.

Several other comments endorsed an approach of a broad CDRH guidance providing generalized criteria for how the Center would respond to new scientific information coupled with targeted communications to affected parties concerning how the agency would respond to specific new information. One commenter stated that FDA should establish reasonable effectiveness dates before implementing guidance or standards resulting from CDRH's analysis of new science, and any such standards or guidance should not have retroactive effect.

The emphasis on a risk-based regulatory approach also informed comments on CDRH communications about new scientific information. One member of industry stated that FDA should develop a risk-based policy about when it would use different forms of communication, advocating formal web notices and letters to industry, as well as labeled warnings and precautions to communicate new information about "high-risk" devices. This comment suggested that information about low- to moderate-risk devices could be communicated by guidance documents or bulletins.

One suggestion for use of a process for communicating new information not currently used by FDA came from a nonprofit group, which advocated use of "Open Door Forums" similar to those used by the Center for Medicare and Medicaid Services (CMS) to engage providers and other members of the public in interpreting new scientific information.

Regulatory Tools. Comments from industry and trade groups generally advocated that CDRH use postmarket and compliance-oriented tools to address new scientific information about devices rather than increasing premarket review requirements. A comment from a nonprofit group urged the use of public notices and safety alerts to inform the medical community of serious safety concerns about older devices, and noted FDA's "extensive" authority to take action to respond to new evidence altering a device's risk/benefit profile. One comment stated that FDA has not used the MDR system well and advocated that FDA develop a system of quarterly reporting for low-risk malfunctions to permit greater focus on more significant adverse events.

Two comments from nonprofit groups stated that, based on new information, FDA could implement new reporting requirements or withdraw a device from the market, and stated that particularly in pediatric populations, regulation must assure the safety and effectiveness of a device over its entire life. These comments advocated changes to premarket evidentiary requirements when warranted by new information.

One comment expressed concern that the case studies presented by CDRH for discussion focus on public health concerns raised by new science and technology, rather than the benefits and asked that FDA take steps to ensure technological improvements are not delayed by "irrelevant outdated" regulatory requirements. The comment referred specifically to the reclassification and de novo processes as areas in need of reform to encourage the best use of new science.

B. Adapting to Novel Technologies or Novel Uses of Existing Technologies

Premarket Review of Novel Technologies. Many comments acknowledged the importance of CDRH's premarket authorities in adapting to novel technologies and novel uses of existing technologies. A member of industry recommended the use of pre-IDE meetings to introduce FDA reviewers to novel

technologies and lay the ground work for discussions on how the technology should be reviewed, a proposal that was echoed in internal FDA comments. One comment observed the importance of appropriate classification of devices at the outset; another comment stated that a higher bar should apply to classifying new technologies as 510(k) devices. Although many comments suggested that CDRH's premarket decision making should account for concerns raised by the novelty of a new technology, one comment noted that the regulatory standard of "reasonable assurance" does not permit CDRH to reserve marketing approval or clearance to only "the best" or "the safest" products. One nonprofit also suggested that, although clinical data may be needed in some cases, quantitative metrics could be used to assess the new technology when the differences between the products are well-defined physical or engineering differences that do not rely on anatomical or physiological factors.

Some comments offered opinions on whether improvements in technology should affect the availability of old technologies as predicates. One comment suggested that 510(k) submitters should include in their submissions a justification for citing an old predicate if new devices that are potential predicates exist. Another comment stated devices should only be removed from the market if proven to be unsafe.

Many who commented expressed concerns about the consequences to consumers of delaying access to novel technologies. Comments expressed a particular concern about the perceived burden of requiring clinical studies for new technologies, and noted, apparently referring to possible study designs for 510(k) submissions, that direct clinical comparison of one device to another is not required by law. One comment remarked on the "almost insurmountable" challenge of recruiting large numbers of ill patients to daily clinical therapy sessions, and asked about the use of a non-blinded study design to study home use of monitoring equipment against an "intent to treat" group as a control.

Risk-Based Decision Making. Comments noted that novelty is one consideration in conducting a risk/benefit analysis and generally favored a risk/benefit approach to considering unfamiliar technologies and uses; however, one trade organization argued for discounting risks presented by uncertainty because CDRH "cannot be held to an impossible standard of accurately predicting every possibility." Another comment advocated additional risk-control measures for first-of-a-kind devices, particularly involving new biomaterials, such as special training for clinicians or new mechanisms to monitor devices in the global marketplace. Others argued that CDRH should use labeling, clinician training, and post-approval studies and other postmarket authorities to address concerns about novel technologies, stating that a requirement of extensive clinical studies in premarket applications would be detrimental to innovation. Some comments argued that a risk-based model would lead to a different approach for in vitro diagnostics than for other devices.

The Role of the Market. Some comments suggested that CDRH's regulatory role in removing superannuated technologies should be limited because market forces will ensure the adoption of improved products as they become available. A comment noted further that older technologies may cost less or be more familiar to certain users; others expressed the view that first-generation technologies should be removed only if proven to be unsafe. Comments noted that clinicians are in a better position than CDRH to determine the continued need for a device, and that different device designs may meet the needs of different practitioners and patients. One comment recommended that FDA take no action to address effectiveness issues with marketed devices, arguing that the market will decide because comparative effectiveness will be determined by third-party payers.

Pediatric Populations. Comments noted the unique challenges as well as unique promise of novel technologies in the treatment of pediatric conditions. These comments advocated "innovation in FDA

regulatory processes" to match the potential of innovative technologies, including collaboration with clinical experts to identify conditions of special concern in pediatric populations and experts in novel device technology during the review of applications. These comments cautioned against the extrapolation of adult data to children.

C. Enhancing CDRH's Technical Competency and Analytical Capability

Areas of Expertise. Although many comments suggested means of enhancing the Center's technical competency and analytical capability, comments differed on the types of expertise they believed to be lacking. One comment distinguished between knowledge and expertise, arguing that CDRH was less in need of scientific expertise than of understanding about the development and manufacturing processes of the device industry. This comment stated further that CDRH should focus resources on developing knowledge about regulatory concepts, such as 510(k) and premarket approval application (PMA) review standards, valid scientific evidence, and least burdensome methods. A trade organization echoed the need for clearer understanding within CDRH about statutory and regulatory policies.

A number of nonprofit organizations commented on the need for particular types of expertise. One group suggested that CDRH seek opportunities to learn from the experiences of advanced practice nurses, who use certain medical imaging and anesthesia technologies in direct care. Several organizations identified a particular need for expertise related to pediatric conditions and therapies for such conditions. These groups expressed support for CDRH's plans to hire pediatric expertise; two of them recommended that CDRH hire a pediatric interventional cardiologist. Other groups suggested that the Center include pediatric subspecialty expertise in all Offices and Divisions of the Center to ensure that pediatric experts participate in all product evaluation and compliance activities. These groups recommended further that CDRH increase collaboration with external groups devoted to pediatric health issues and asked for enhanced representation of pediatric subspecialties on CDRH advisory panels.

Means of Improving Expertise. Several comments from industry encouraged CDRH to interact more with industry representatives to enhance the Center's knowledge of new technologies. These comments recommended that CDRH increase opportunities for researchers and product developers from industry, academia, and the health fields to present new technologies to CDRH and that CDRH staff participation in such training be encouraged. One comment advocated mandatory CDRH attendance at industry and standard setting meetings. Another comment approved of FDA's practice of using outside experts to review high-risk novel technologies presented in PMAs. A trade organization summarized existing practices for leveraging external expertise, including contractual use of experts in products reviews, use of Cooperative Research and Development Agreements (CRADAs) with industry, and recruiting fellows into the Commissioner's and Center Fellowship programs, and suggested CDRH increase its use of these practices. This group also suggested that CDRH use trade organizations to poll industry about gaps in internal expertise.

Other nonprofits provided suggestions for new mechanisms of acquiring expertise. One nonprofit advocated a "regulatory site training program," providing an opportunity for CDRH staff to visit manufacturers of high-risk or novel devices and hospitals. Another nonprofit suggested that federal agencies and scientific organizations collaborate on the development of an "independent Technology Assessment Institute" to evaluate medical imaging and radiation therapy products, and to develop procedures and guidelines for the use of existing, new and advanced technologies.