Protecting the core of CDRH regulatory science in the face of financial and strategic threats

A report of the Science Board to the FDA

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1. Executive Summary

Regulatory science and engineering at the FDA's Center for Devices and Radiologic Health has saved lives and protected the Nation for decades. CDRH is blessed with outstanding human resources (the scientists and engineers at FDA perform at a high level and balance their regulatory and research roles because of their passion for the work) and an outstanding physical infrastructure (the laboratory and equipment environment exceeds many research universities and is to be commended). In the face of an evolving landscape of regulatory sciences, increasing pressure on regulatory agencies to simultaneously ensure safety and enable access to emerging technology, and major financial and strategic challenges to FDA, the Science Board of the FDA created a subcommittee that reviewed the mission and strategy of CDRH science and the ability of the organization to continue its pivotal role.

Loss in federal investment in regulatory science at CDRH will interfere with the regulatory approval of emerging technologies and in doing so cost lives. With the medical device industry setting a record pace in advancing life-saving technology there is no more pressing need at the FDA than to fund fully a robust and successful CDRH regulatory science program. This report summarizes how that investment might best be utilized but nothing in this report should suggest that there is any room for cost cutting in this program. Indeed, it could be argued that increased funding and focus of the program would save even more lives.

After two site visits, interviews and visits with CDRH leadership, directors of all of OSEL and OSB Divsions, leaders of the individual laboratories, tours of the facilities and consideration of a large amount of data and information, this report describes our consensus view that the shifting demands CDRH necessitate rapid change in the organization and more specific focus. Each of the issues confronting FDA requires that scientific excellence at CDRH must be aligned to regulatory science. Only scientific excellence in the domain of regulatory science can directly meet the expectations of CDRH, place CDRH at the forefront of the evolution in regulatory sciences, and since the current portfolio of science at CDRH includes programs beyond this scope, the existing spectrum of projects is not sustainable in the current environment. We advocate for continued vigilance about the need for a focus of CRDH on research that directly impacts regulatory science and serious consideration of reorganization in structure and leadership in the research arm of CDRH and in particular OSEL to achieve this goal.

Over the last decade a variety of external reviews and FDA responses have suggested the need for CDRH research to be tightly coupled to its regulatory mission. Although the Center Director and his key Associate Director carefully and eloquently described the core mission and strategies for research at CDRH, it was not clear that these fundamental building blocks of tactics and organizational structure have fully penetrated across the whole of CDRH's research team. The sub-committee was confronted with some members of the research team providing different explanations of the mission statement that spanned the extremes from concentration on science in support of regulation to science in search

of expanding disciplinary excellence. In addition, there was insufficient clarity regarding to what extent research should be directed to support reviews.

Although finance and budget were not a specific part of the sub-committee's charge, any review of research preparedness and appropriateness must be related to income and expenses. The committee was presented with a number of budgetary summaries but was unable to ascertain how strategy was connected to budget, existing programs will meet budgetary limitations, emerging programs will be funded and prioritization is based on adherence to mission. However, we understand that more recent changes to the Center's science prioritization process have more closely linked the criteria to mission, vision and public health impact. This review did not evaluate those changes because they were implemented towards the end of the review.

All research organizations operate on limited funds. The sub-committee found that in the last 5 years the annual budget for research has experienced an apparent shift from "non-competitive" funding to "competitive" funding. Until recently, the majority of the program was funded in a manner that was unrestricted in focus. Now, the program is apparently mainly funded from sources that direct the research program to particular goals (Medical Countermeasures, Women's Health, Critical Path Initiative etc.) and many of the staff are supported for tenures of two years or less. This apparent change in revenue sources and the churning that can come from short-term appointments can be a benefit but only if the research strategy is fine-tuned to fit this new reality. The advent of the public-private partnership through MDIC emerged as we were completing our report and we were not provided with insight into how participation by FDA will benefit CDRH and how OSEL scientists are expected to participate in and take advantage of this initiative. The stark reality is that all federally supported research programs are likely to face major reductions in funding in the coming years. CDRH must immediately focus its endeavors in such a way as to absorb the inevitable changes in how they invest in regulatory science. Prior reviews of CDRH research have suggested similar or identical needs, but those prior reviews were produced in response to different challenges and opportunities.

The research arm of the Center requires strong permanent scientific leadership that is aligned with mission and the realities of achieving that mission in a complex environment. Although the individual leaders of science at CDRH are capable and dedicated to the FDA and their units, there is not sufficient alignment across the research components in OSEL to a shared strategy. There was an apparent significant difference in approach between the two primary research arms of CDRH, OSEL and OSB. The management of the Office of Surveillance and Biometrics (OSB) made it clear that it focuses on providing epidemiological and statistical expertise in innovative approaches to observational studies and clinical trial designs and provides consultants for CDRH reviews through ODE. In contrast the subcommittee was left with the impression of within OSEL there can be a drift away from a mission-focused endeavor. Many of the comments are, therefore, directed to OSEL. The available budget and tightly-focused need may not be commensurate with having 20 Laboratories and 6 Divisions. This may well have been the correct strategy for the past and one promoted by previous leadership but in the face of today's unique pressures the current approach may not be sustainable and may not be optimally suited to address important regulatory science issues pertaining to emerging technologies. The organizational structure of OSEL evolved for good reasons but should be re-evaluated to assure it is effectively focused on

regulatory science for which CDRH is uniquely situated to perform or by necessity must perform, and make appropriate changes to the organization.

The sub-committee strongly recommends that CDRH should invest internal resources in regulatory science and engineering: science that no other organization is equipped for or capable of performing. This latter point cannot be over-valued and exists irrespective of budgetary limitations. That said, there is always a role for forward looking basic research when resources are available. Naturally, if no other organization is capable or willing to do a research project that is needed for regulatory reasons, then CDRH is obligated to pursue that line of research. The field of regulatory sciences is growing exponentially and FDA scientists can and should play a major role in defining and contributing to this growth. It is vital that CDRH assure that its research organizations be structured in a manner which maximizes the chances of success in achieving its mission. This requires being able to quantify success and measure that against quantifiable goals. The sub-committee recognizes that it is not easy to measure success in research, but we stress that it is a requirement when periodically refining strategy and tactics. Metrics, measures and results should be as ingrained in culture as the strategy and tactics. We encourage CDRH to develop new metrics to measure research productivity and to regularly assess their new metrics to determine if they adequately measure whether or not the Center is meeting its research mission effectively.

In summary, CDRH is at a pivotal point in its investment in and governance of regulatory science for medical devices and radiological health. Strong leadership is essential because CDRH's research organizations, and OSEL in particular, may need to fine-tune their structure to continue to advance the regulatory evaluation of emerging technologies and in doing so protect the public and save lives through their research. Toward the end of this report we provide detailed recommendations but one consistent theme and recommendation can now be provided: the threats to regulatory science at CDRH are extreme and the only effective strategy moving forward is to protect the already underfunded program to the maximum extent possible and to sharply focus the research mission and strategy through an effective organizational structure and portfolio mapping. The outstanding scientists and engineers at CDRH are well equipped to make any necessary transition as long as the federal government maintains its data-driven investment in the health and wellbeing of the public.

2. Introduction

Periodic external review of an organization can serve as a vehicle to reflect upon and identify the organizations' strengths and challenges into the future, and to facilitate change that can improve its effectiveness into the future. In the face of a rapidly evolving medical device industry, the CDRH is charged with insuring the public safety, while simultaneously enabling new innovations to reach the public. This challenge necessitates working with and serving a range of stakeholders from consumers to medical practitioners to industry.

CDRH is threatened in its mission by the enormously rapidly evolving range of technologies as well as newly emerging cultures that have a greater capacity for innovation that ever. CDRH seeks to have an effective mechanism for review through coupling its regulatory scientists, who are trained in areas of science and engineering, with review personnel. Regulatory scientists focus their studies on those issues which facilitate the review of new products and medical devices, which are necessary to evaluate the safety of those new technologies.

There is a delicate balance between the rapid introduction of new and innovative products and the protection of the public safety. In making decisions, CDRH must identify relevant scientific issues, develop and collect evidence to address the issues, and then assess and judge the evidence. If CDRH is to do this effectively, its regulatory scientists must maintain their scientific expertise and be poised to adapt to new scientific and technical challenges for the future. In the face of the rapidly expanding knowledge base, this is a challenge for any organization. It is particularly challenging for a regulatory agency which does not have the luxury of selecting which of many aspects of science it must have expertise; it must have adequate coverage in all.

Budgetary uncertainties faced by the Center make the balance between approval of new products and protection even more precarious. As Congress and the Administration balance the budget by shrinking government, CDRH must justify resource needs. However, newly emerging technologies require that the staff keep pace with an ever increasing and more sophisticated technology base, more innovative products, and an increasing workload. New knowledge must be acquired and assimilated into the review process to make confident decisions on new medical devices. These challenges are ones that live under the public and congressional scrutiny on a daily basis, creating stress for the Center.

To help assure the quality and relevance of the Agency's regulatory decisions, the FDA Commissioner has directed CDRH and the other FDA Centers to examine how science is used in their respective organizations. This includes an assessment of whether the needed scientific expertise is available currently, whether it is effectively used, and a determination of the scientific expertise needed for the future. This has led to the external science review presented in this report. The Subcommittee appointed to conduct this review, and which has authored this report, hopes that its findings and recommendations will be of service to FDA and to CDRH in directing its future.

CDRH scientists are excellent and dedicated, and are making significant contributions in an increasingly challenging environment. Some are directly responsible for making regulatory decisions, others serve as consultants to the regulators on an as-needed basis but they also conduct research deemed beneficial to public health. In the past, research topics were selected primarily by scientific interests and there was little evident effort to achieve coordinated goals. More recently, there has been a new trend toward

ensuring that research topics address problems with clear relevance to regulation; the phrase "regulatory science" was apparently coined to refer to research with such relevance. As part of the trend, formal processes have been developed and tested to prioritize research.

3. Subcommittee Charge and Objectives

Charge to the CDRH Research Review Subcommittee

The Center for Devices and Radiological Health (CDRH) is responsible for promoting public health by facilitating medical device innovation and protecting public heath by assuring that medical devices are safe and effective. CDRH regulates a wide range of products from tongue depressors to cardiac pacemakers, imaging equipment to in vitro diagnostic devices.

CDRH Vision for Regulatory Science: CDRH's regulatory science research program is designed to be proactive, by anticipating regulatory and public health issues, and responsive, by focusing on important and emerging public health and regulatory issues. Our research is highly relevant to Center's regulatory needs, collaborative, of high quality, and integral to the Center's regulatory mission and public health portfolio. Our regulatory science research portfolio consists of multidisciplinary laboratory research programs in our Office of Science and Engineering Laboratories (OSEL), multidisciplinary regulatory research projects in pre- and post-market offices, and epidemiological and statistical research in our Office of Surveillance and Biometrics (OSB). The regulatory science research is conducted in-house and through collaborations with other Federal organizations, other FDA Centers as well as industry, health care professional organizations, and academia both in the U.S. and abroad. This research provides CDRH with scientific expertise, tools, standards, methodologies, and data to support science-based decision-making and policy development as well as help industry develop, assess, and manufacture new devices and technologies more quickly and efficiently.

Charge to the FDA Science Board: The FDA Science Board was charged with conducting a review to assess how CDRH's regulatory science portfolio can best anticipate and address emerging medical devices and new public health concerns from currently marketed devices. The subcommittee should consider the broad scientific disciplines and technologies that CDRH needs to support its regulatory functions and decision making.

Specifically, the Board was asked to address the following questions:

- What, if any, changes should CDRH make to its regulatory science research portfolio to best accomplish its public health mission?
- Given the breadth of devices before us and what is anticipated in the future, what should be CDRH's capacity for conducting or collaborating on regulatory science research?
  - Assess any gaps in regulatory science capabilities or expertise.
  - Identify scientific areas where CDRH should make programmatic and resource changes.
  - Identify opportunities for collaboration to better leverage CDRH's regulatory science programs.
- A growing challenge for CDRH is to assure that the Center is optimally prepared to facilitate the development, review, and monitoring of new and emerging medical technologies. What methods, such as horizon scanning and research prioritization, should be used and how could they best be employed to optimally preparing the Center to address new and emerging medical devices?

4. Process of Review

The review of individual FDA Centers by subcommittees of the FDA Science Board began in 1998. CDRH was reviewed in a comprehensive manner in November 2001. That review focused on CDRH's use of science and scientific expertise, its overall structure and its readiness for the future. A comprehensive set of recommendations and concerns emerged and CDRH leadership updated progress in 2007 through a detailed response to the subcommittees work. In 2008, as part of the FDA Science and Mission at Risk report process, Center leadership reflected further on the 2007 update. After a decade of changes and reflection on the 2001 report it was time to once again perform a comprehensive review of science at CDRH.

At the 2011 Science Board meeting the FDA established a sub-committee for a comprehensive review of the role of research and science at the Center for Devices and Radiologic Health. As described in the prior section, the Science Board was charged with conducting a review to assess how CDRH's regulatory science portfolio could best anticipate and address emerging medical devices and new public health concerns from currently marketed devices. The subcommittee decided to pursue this charge by reviewing the ***organization, quality, responsiveness and foci of science within the Center***. The subcommittee consisted of seven members who represented a cross section of the expertise needed to assess CDRH research programs and environment.

The broader context for this review is, of course, the ongoing pressure on CDRH to reduce costs while simultaneously increasing the pace of regulatory decision making. The subcommittee cannot change the contradictory objectives of Congress's desire to invest less in regulatory science but generate increasingly rapid science-based results, but it is clearly the case that Center leadership must have a strategic plan that places and protects regulatory science at the core of the endeavor. Our review, therefore, represents a snapshot of the plan and execution but we recognize that the shifting Congressional and Executive Branch leadership and goals make that plan outdated on a regular basis. We therefore were particularly interested in the scientific agility of the structure and leadership at CDRH.

The initial step in the review process was to ask CDRH to work on a Strengths, Weaknesses, Threats and Opportunities analysis for science at CDRH and to provide the subcommittee with as much information as possible concerning prior reviews, responses to recommendations and ongoing strategic planning. The subcommittee then formulated an agenda for an initial site visit that flowed from observations made on the very detailed material provided. During the initial visit the subcommittee focused on how research was organized at CDRH, how CDRH anticipated and responded to new emerging technologies, how the mission was communicated inside and outside the FDA community and what quantifiable evidence was available that supported the need for investment in research at CDRH. The initial site visit led to many more questions which were summarized in a detailed letter from the subcommittee to CDRH leadership. These questions led to a large amount of work at CDRH and to the generation of a large amount of data and information. The subcommittee deeply thanks all the people that worked so hard to respond to the initial observations so completely. The initial observations likely led to some new ideas and activities and the subcommittee felt that a second site visit would be important. This second

visit was focused more intently on identifying the strategy and vision for the program and interviewing individual scientists to learn about how decisions are made and communicated. The subcommittee invested considerable time seeking to understand whether the research being pursued at CDRH was unique research that no other organization would perform if CDRH were not to have an intramural research activity. More importantly, the subcommittee sought to understand whether that research would be critical in future regulatory decision making. Subsequent to our second site visit the subcommittee requested more details on an emerging public private partnership and on an emerging strategic plan. The first draft of this report was completed while awaiting that documentation.

a. CDRH Preparations for Review

i. Prior review conclusions

The 2001 FDA Science Board report on Science at Work in CDRH had fourteen final recommendations that flowed from concerns and observations. Although the 2008 response describes many sincere actions taken to address the issues raised, our 2012-2013 review identified many of the same issues. For completeness and emphasis we therefore list the recommendations from the 2001 report below (the emphasis is ours). In the subsequent section we then comment on the actions taken at CDRH in response to these 14 recommendations and assess to what degree these actions were successful. At its simplest the prior recommendations were that CDRH needed to **optimize its organization of science to meet its mission, communicate more effectively with all stakeholders, collaborate more fluidly, become scientifically agile, nurture the intellectual talent of scientists at CDRH and, create a strategic staffing plan**.

- CDRH needs to ***communicate***, both internally and externally, a clear vision of the fundamental role of science in the regulatory process. This vision should define the role of science in developing relevant guidance documents and in developing, modifying, and approving appropriate standards. The vision should delineate the role of science in determining how effectively CDRH responds to new technologies and facilitates the introduction of those technologies to users in a safe and effective manner. ***Development of a system for summarizing the scientific and other factors*** leading to guidances or approvals (or rejections) would be useful both for FDA, as it reviews its decisions, and for the public.
- So that science can play this fundamental role, CDRH needs to rethink how it carries out its mission, prioritizes its activities, outsourcing those functions it can while still maintaining oversight, and reallocating its resources so as to expand its investment in science, in all Offices. As part of this rethinking, CDRH should ***examine its existing organizational structure*** as well as other regulatory models, with consideration for change to implement and support the TPLC concept. Given fixed budgetary constraints, one model would be for FDA to focus its inhouse expertise on selected tasks, and delegate others to official notified bodies or similar entities that derive funding from non-governmental sources.
- As part of its restructuring of activities to enhance the fundamental role of science, CDRH should assess and reconsider the structure of OST to focus on emerging science and technology; this assessment likely will require a separate review of OST.
- CDRH should develop a plan ***for enhancing cross-office and inter-agency*** (e.g., FTC, FCC) communication and collaboration.

- CDRH should establish an ***electronic database*** for liaison functions and internal and external expertise inventory.
- CDRH should develop and implement a ***formal process for capturing institutional knowledge*** through more time spent on guidance documents, standards, other written publications, and archiving and retrieval systems, with written precedent files so that when a decision is reached it does not only remain in the "mind" of the reviewer. Professional recognition and credit should be given to the contributors, and the contributors should be rewarded.
- In recognition of the large staff turnover anticipated in the next 5 years and in order to fill gaps in scientific expertise, CDRH should expeditiously perform an assessment of the current level and breadth of expertise and use this to develop a long-term ***strategic staffing and recruitment plan***. Major gaps in expertise should be identified and filled during recruiting for staff replacements due to attrition and turnover. For each position, the options of full-time, part-time, or contract (external) personnel should be considered.
- CDRH needs to develop procedures and implement ***staff development/training opportunities*** to ensure that reviewer mandates for such issues as sample size or randomized trials are shaped by realistic clinical perspectives and relevant ethical considerations.
- In recognition of its staff being its greatest resource, CDRH needs to streamline processes that ***encourage scientific growth*** within the staff and the maintenance of scientific expertise; these processes need to provide for a more inviting career path and a reward structure for scientific personnel, and will require a reallocation of budget resources so that stated goals of staff growth can occur.
- CDRH should encourage and facilitate the ***use of internal but non-ODE expertise and also external expertise***, including the development of operational and budget policies that promote a more liberal use of external experts.
- CDRH should expand its ***outreach to and scientific interactions with industry and universities*** through visitor programs and the creation of appropriate forums for professional development and for information exchange between FDA staff, industry, and academia with particular emphasis on new scientific fields that may result in new medical devices within the next 5 years.
- CDRH should develop a plan in collaboration with other Centers for the evaluation of ***combination products***; this plan may require changes in organizational structure and operational procedures. Whether it is a new structure or some amalgamation of existing structure, the regulation of these products requires an approach that is least burdensome and embodies the philosophy of CDRH.
- CDRH should develop and implement a quality evaluation and improvement program, and as part of this, the evaluation system should ***develop metrics for the assessment of quality as well as the timeliness of results***. The focus of these activities should be to achieve high quality product reviews in a timely manner. Management should implement a system for recognizing, rewarding, and encouraging high quality product reviews and investigations.
- CDRH should implement a quality system with both continuous evaluation and improvement programs in accordance with ISO 9000 or other relevant standards. The focus should be on CDRH as an organization with a specific mission and on the development of activities that contribute to high quality decisions making the most productive use of resources and with a high degree of consistency.

ii. Responses of CDRH to prior reviews

As mentioned above, the 2001 report strongly recommended that CDRH **optimize its organization of science to meet its mission, communicate more effectively with all stakeholders, collaborate more fluidly, become scientifically agile, nurture the intellectual talent of scientists at CDRH and, create a strategic staffing plan**. In 2007 CDRH produced a very detailed set of actions taken to address those needs. These are summarized below.

> *Optimize organization of science to meet mission*. CDRH created the Office of Science and Engineering Laboratories to bring its 20 some laboratories under a cogent structure, and initiated a complex science prioritization process in order to determine how to distribute the funds at its disposal. The structure may well have been an appropriate first step, though it is a complex and highly diversified structure for the available budget.
>
> *Communicate more effectively with all stakeholders*. A variety of attempts to enhance internal and external communication strategies was described.
>
> *Become scientifically agile*. Horizon scanning was recognized as essential to the regulatory mission of CDRH and it was recognized that this should be an ongoing effort.
>
> *Nurture the intellectual talent of scientists at CDRH*. CDRH described a number of training and seminar opportunities that were being made available to staff.

A somewhat more explicit view of the recommendations that flowed from the 2001 report (which were then updated in 2007 in the FDA Science and Mission at Risk document) appeared in a draft document from 2008 that CDRH prepared to respond to the 2007 recommendations. In this 2008 draft the CDRH response observed that a different environment had emerged and took a position that challenged many of the 2007 recommendations. This document was revised in 2011 and shared with the subcommittee but did not become an official response. Summarizing approximately 200 pages of study and responses in 20 lines within this report naturally leaves out all the rich detail that explains the prior report and responses to it. **Importantly, since our report concludes with a similar set of conclusions it would appear that much work is still to be done to address concerns that threaten the future of CDRH research programs given the strategic and financial extremes that are now upon us. Indeed, in very many respects these outstanding issues have become more acute over the last decade by virtue of the increasing complexity of the regulatory landscape, the continued growth of knowledge and sophistication of submitted technology and supporting information that must be mastered and the concomitant fiscal constraints that will inevitably drive CDRH research budgets down**. It is important to restate that although our recommendations mirror those made in the past, CDRH did respond to prior recommendations with actions and change. The reality is that as they responded the ground was constantly shifting and now, ten years later, we find ourselves in a position where similar recommendations and changes are still appropriate. This implies that focus, communication, excellence and engagement will always serve the community well and can always be improved.

iii. Self-analysis of strengths, weaknesses, opportunities and threats

The following SWOT analysis was performed by the CDRH as they prepared for the first site visit of our sub-committee. Importantly, this report was not sanctioned or distributed within FDA and was generously provided in response to the sub-committee's requests. Although it is an unofficial report is is excellently thought out and it was so informative to the sub-committee that it is included in our final report verbatim.

Strengths [as described by CDRH]

As measured in recent staff opinion surveys, our scientific staff is strongly motivated to fulfill our public health mission. CDRH's mission of protecting public health by assuring the safety and effectiveness of medical devices and the safety of radiation emitting products while facilitating innovation of medical products is a powerful driving force for our scientists and engineers. Our team includes highly regarded scientists with a wide array of experience and expertise in relevant areas of regulatory science including biology, chemistry, engineering, mathematics, statistics, physics, computer science, modeling, clinical practice, and epidemiology. This breath coupled with our strong record of science and engineering outputs, including peer-reviewed publications, technical reviews of regulatory submissions, standards development, guidance documents, and presentations at national and international meetings, has earned us the respect of many in the medical device, science, and engineering communities. While we often face challenges recruiting new scientific expertise and maintaining the depth of expertise needed, our motivated core scientific team is one of our strengths.

In addition, we have built a reputation for conducting high quality research that answers public health needs and that may not be possible to conduct any other place in the nation. From our MDEpiNet program that brings together medical device epidemiology experts from across the country to study pressing medical device health concerns to our partnerships with TSA, FCC and other federal agencies to make sure new technologies are compatible with medical devices, CDRH has a unique role to play in assuring the safety and reliability of an important part of the health sector.

Our research and our researchers directly inform the regulatory process and decision making. Because we are able to uniquely interact with manufacturers and the pre- and post-market data they generate while maintaining proprietary confidentiality we have unique access to innovative devices and device data that other research centers do not. And we are able to use these resources in partnerships with many external scientific stakeholders in both the public and private sectors.

Weaknesses [as described by CDRH]

In general, our scientific weaknesses fall into 3 categories: capacity, legal/regulatory including issues with collaborations, and access to/availability of scientific information.

Capacity

On the capacity front, we have difficulty assuring a consistent flow of resources- human, financial, and material capital- necessary to accomplish our public health mission. For example, we have difficulty attracting, hiring, training, and retaining the highest quality scientific personnel. The federal hiring

system can add months to the process of attaining any new hire. The federal pay scale may allow us to offer salaries competitive with academic positions, but can make it difficult to recruit private industry researchers. Training is generally geared toward reviewers rather than researchers and opportunities for continuing education and professional development are limited by budget and having a sufficient number of review staff to allow staff to engage in training opportunities while assuring timely completion of our work. This can reduce the opportunity for our scientists to attend informative meetings to learn about a new field of research. Finally, retention is sometimes limited by advancement opportunities and necessary regulatory consult demands. Pay freezes can make retirement an increasingly attractive option for our aging scientific workforce.

Financial resources have also been a challenge in recent years. We would like to conduct more proactive and ground breaking scientific research since we rely upon this regulatory science work to prepare us for responding to emerging technologies and unforeseen public health needs. Also, advances in regulatory science can facilitate device innovation by informing the development of safer, more effective, higher quality devices as well as reduce the time and cost of device development, assessment, and review. In addition to the overall level of funding, the funding uncertainties we face further constrain our efforts. Multi-year scientific funding would be ideal, but it is rare in the federal government. However, even single year federal funding has become more complex in recent years. Budget uncertainties impact morale. Delayed Congressional budget cycles (fiscal year begins October 1, but budgets are often not passed out of Congress until several months after that) and annual internal FDA contracting deadlines (e.g. no new contract for over $150,000 for the year after May 1) leaves a very short window to compete and bid the large research contracts that we rely upon to supplement our internal research capacity with extramural expertise.

These contracting restrictions also impact our access to material resources needed to perform intramural research. Large scale scientific equipment purchases, IT hardware, and software improvements are affected by this as well. An increasing shortage of lab and office space and delayed lab equipment installation are at times problematic. IT security concerns can also slow the implementation of new systems.

There are conflict of interest issues when laboratory scientists conduct collaborative research with companies whose products are under review in the Center. Specifically, researchers are not allowed to participate in those reviews or consults that involve collaborative research results to avoid conflict of interest. This issue presents problems of finding the right expertise to review products that incorporate new technologies.

<u>Legal/regulatory, including issues with collaboration</u>

While our regulatory mission makes us a critical part of assuring the nation's health, it can sometimes make it more difficult to complete our regulatory science goals. FDA is very careful to monitor our interactions with regulated industry and this can sometime slow research collaborations and flow of scientific expertise.

We do not conduct external collaborations without relevant material transfer agreements, confidential disclosure agreements, research collaboration agreements and/or our technology transfer agreements in place. In addition, we rely upon our research staff to perform consults to supplement the scientific expertise in our review divisions. We work very hard to firewall off researchers from participating in

reviews that too closely touch upon their scientific research. This is more difficult when our subject matter expertise is one scientist deep.

Access to scientific information

We have three main barriers to accessing scientific information in the Center. First, our regulatory concerns also make it more difficult to obtain access to external scientific expertise. The Federal Advisory Committee Act requires that when we want several outside experts to provide their opinion or consensus advice they must be serve as Special Government Employees (SGEs) as part of chartered federal advisory committee. The 6 to 12 month lead time required to obtain new SGEs can make it difficult for them to be useful in answering questions related to new fields of science or unforeseen health crises and the time and cost of holding advisory committee meetings limits their utility.
Second, we need to improve our knowledge management systems to better access knowledge and expertise previously generated within the Center. As our workforce ages and retires and our turnover rate remains high, it is critical that we improve these processes.
Finally, we need better systems in place to track our research and capture our scientific output, impact, and use of resources. A Center-wide database of research projects, funding, and effort would help us more accurately track trends, needs, and gaps.

Opportunities [as described by CDRH]

There are several recent shifts in the FDA and the medical device landscape that make this an ideal time to improve and expand our regulatory science efforts.
First, there is a growing public and industry interest in regulatory science, particularly as it impacts medical devices and utilizes engineering. Establishing the FDA Science Board subcommittee on engineering at the FDA and the recent Agency reports on regulatory science and innovation demonstrate the FDA's emerging interest, but we have also observed a growing number of requests from industry and academia to partner with us on new regulatory science initiatives. This could spur a new generation of medical device public private partnerships to help synergistically tackle some of the more important research questions. New Center-wide initiatives in computer modeling and molecular imaging are attempting to harness that enthusiasm. And this enthusiasm and growth is not just restricted to the lab sciences. Recently, we have seen enormous opportunities in public-private partnerships via MDEpiNet, to allow us to better prioritize and address a multitude of public health issues, methodological needs, and infrastructure development concerns.
Second, the recent medical device user fee negotiations provide an opportunity to generate new interest in our scientific mission. While the focus of these discussions has been on review resources there also seems to be some understanding among the stakeholders that regulatory science and CDRH scientific expertise also has an important role to play in getting safe, effective, and innovative medical devices to patients as rapidly as possible.
Third, we are on the cusp of establishing a new set of scientific tools to help us revolutionize epidemiological research in medical device-related areas. Unique Device Identifiers (UDI), electronic health records, new analytical tools, and electronic submissions will allow us to more rapidly identify

and mitigate new risks, more accurately determine the frequency of known adverse events and reduce the time and costs to obtain data to support the pre-market review of some devices.
Fourth, our continued leadership in scientific computing within FDA has brought additional attention and resources to these longstanding efforts. CDRH has recently become the focus of the Agency's medical counter measure-related computing efforts. These projects are just getting off the ground. The emerging information age is the perfect complement to our existing computing and engineering strengths.
Fifth, three new projects may address some of our weaknesses. Our recently launched Network of Experts program is designed to streamline our access to external scientific expertise and the Center's Knowledge Management initiative should provide our staff with better tools for developing, recording, storing, and sharing scientific knowledge. In addition, the formation of the Center Science Council has provided a central CDRH forum to discuss and incorporate advances in scientific knowledge into our Center-wide processes.
We are also seeing increasing harmonization with other Federal agencies having common interests. For example, TSA for assuring safety of airport security devices, DARPA for long-term safety and reliability of neural implants, and NIH for standardized phantoms for clinical imaging studies.
Center's newly initiated "Innovation Pathway" program is expected to offer another avenue for finding and getting needed scientific expertise on new questions on new technologies and complex devices.

Threats [as described by CDRH]

The biggest threat to accomplishing our scientific mission is the rapidly increasing complexity of medical devices and the science that underlies their design. We must ensure that our scientific personnel stays abreast of the latest scientific developments and that our recruitment and program planning efforts anticipate emerging needs. We must remain flexible while continuing to address long-term scientific questions and needs.

Furthermore, today we face a very challenging political and economic environment. Critics would like us to reduce our regulatory and scientific efforts and there is little appetite for the revenue increases needed to expand our scientific efforts. The following are some specific example resulting from this environment:

- OSEL research has the potential to suffer from changing economy, changing political environment, user fee negotiations, inability to handle increasing complexity of devices, and others.

- OSEL's regulatory research is not a part of device legislation; hence, its budget becomes discretionary. Complementary issue that arise as a result, such as:

- Perception in some CDRH offices that research does not serve Center's mission needs,

- Perception in some public arenas that OSEL does not add any value to medical products.

- Lack of awareness of OSEL work by outside entities

iv. Emerging CDRH strategic plan (Taken from FDA web site)

PRIORITY 4. PROACTIVELY FACILITATE INNOVATION TO ADDRESS UNMET PUBLIC HEALTH NEEDS

CDRH will further enhance our efforts to anticipate emerging technological trends and public health challenges and partner with federal and external stakeholders to facilitate the development of innovative, safe and effective medical devices and advance regulatory science.

Strategy 4.1. Foster the Development of Innovative Medical Devices

CDRH will work with our federal government partners and external constituencies to facilitate the development of innovative, safe and effective medical devices.

Goal 4.1.1. By September 30, 2012, CDRH will create processes and tools that will improve the pipeline for innovative medical devices and transform the way CDRH works with medical device innovators.

By March 31, 2012, using the Entrepreneurs in Residence Program, begin to pilot the Innovation Pathway 2.0.

By September 30, 2012, assess the implementation of the Innovation Pathway 2.0.

Strategy 4.2. Further Develop a Personalized Medicine Program

CDRH will work collaboratively with our federal government partners and external constituencies to assure the appropriate regulatory oversight of therapeutics and diagnostics when their safety and effectiveness are intimately tied to one another.

Goal 4.2.1. By September 30, 2012, CDRH will continue to develop policies and procedures to assure that safe and effective diagnostic products that are either innovative themselves or provide innovative uses reach the public.

By June 30, 2012, clear within CDRH the final guidance on Companion Diagnostics.

By December 31, 2012, clear within CDRH draft guidance on co-development of drugs or biologics and devices.

Strategy 4.3. Strengthen Regulatory Science

CDRH will work collaboratively with our federal government partners and external constituencies to advance medical device regulatory science.

Goal 4.3.1. By December 31, 2012, CDRH will have in place mechanisms to enable collaborative work between FDA, our federal government partners and external constituencies to advance medical device regulatory science.

By December 31, 2012, establish a public-private partnership between industry, the FDA, and academia to advance regulatory science.

Goal 4.3.2. By September 30, 2012, CDRH will expand computer modeling and simulation efforts to support regulatory science.

By September 30, 2012, finalize a strategy for validating and incorporating computer models that are part of the Virtual Physiological Patient Project into a publicly accessible library that can be used in device development and regulatory applications.

b. Subcommittee Review

i. Subcommittee Membership

Chair: Alan J. Russell, PhD. Highmark Distinguished Career Professor, Carnegie Mellon University, Pittsburgh, PA.

Co-Chair: Elazer Edelman, MD., Ph.D. Thomas D. and Virginia W. Cabot Professor of Health Sciences and Technology at MIT & Professor of Medicine at Harvard Medical School, Cambridge, MA.

Paul Billings, Paul R. Billings M.D., Ph.D., F.A.C.M.G., Chief Medical Officer, Life Technologies Corporation

Warren Grundfest, MD, FACS. Professor, Bioengineering, Electrical Engineering, and Surgery, UCLA, Los Angeles, CA

Peter Katona, ScD. Professor, Department of Bioengineering, George Mason University, Fairfax, VA.

P. Hunter Peckham, Ph.D. Donnell Institute Professor of Biomedical Engineering, Distinguished University Professor, Case Western Reserve University, Cleveland, OH.

Hugh Tilson, M.D., DrPH Adjunct Professor, Public Health Leadership, Health Policy, and Epidemiology, UNC Gillings School of Global Public Health, Chapel Hill, NC 27599-7469

ii. Agendas for Site Visits

Science Board Visit to White Oak
Wednesday, January 4 – Thursday, January 5, 2012
Location: WO-Bldg 32, Room 1321 (unless otherwise noted)
Dial-in: 1-877-918-4543; Leader Passcode: 4874859; Participant Passcode: 8976390

AGENDA

Wednesday, January 4

8:00-8:30am	Center Director's Introduction *Jeffrey Shuren, MD, JD*
8:30-9:00am	Chair and Co-Chair greetings *Alan Russell, M.D., PhD,* *Professor and Chair of Bioengineering, Stanford University* *Hunter Peckham, Ph.D.* *Executive Director, Cleveland FES Center*
9:00-10:00 am	Office of Science Engineering and Laboratories (OSEL) Presentation *Steven Pollack, PhD* *Director* *Joel Myklebust, PhD* *Deputy Director for Science and Strategic Initiatives* *Subhas Malghan, PhD* *Deputy Director for Science Evaluation and Coordination*
10:00-10:15am	Break
10:15-11:00am	OSEL presentation continued
11:00am-12:00pm	Office of Surveillance and Biometrics (OSB) presentation *Thomas Gross, MD, MPH* *Director* *Gregory Campbell, PhD* *Director, Division of Biometrics* *Danica Marinac-Dabic, MD, PhD* *Director, Division of Epidemiology*
12:00-1:00pm	Working lunch- B**ldg. 32 Cafeteria**
1:00-2:00pm	Critical Path Poster session- **Bldg. 66 Atrium**
2:00-3:00pm	OSEL tour- Subhas Malghan, PhD
3:00-4:00pm	Q&A with senior staff led by William H. Maisel, MD, MPH, Deputy Director for Science and Chief Scientist - **Bldg. 66, Rm. 5425**
4:00-5:00pm	Executive session- **Bldg. 66, Rm. 5425**
6:30 pm	Dinner at Blair Mansion Inn Restaurant 7711 Eastern Avenue, Silver Spring, MD 20912

Thursday, January 5

8:00–9:30am	Case studies • OSB: Use of Post-Market Data, including data mining, high performance/scientific computing, and Bayesian statistics *Thomas Gross, MD, MPH, Gregory Campbell, PhD, and Danicia Marinac-Dabic, MD, PhD* • Cardiovascular Computational Modeling/Simulation *Michelle McMurry-Heath, MD, PhD, Associate Director for Science* *Donna Lochner, Acting Associate Director for Scientific Outreach and Coordination, OSEL*
9:30-9:45am	Break
9:45-11:00am	Case studies continued • Next generation/whole genome sequencing *Zivana Tezak, PhD, Associate Director for Science and Technology* • Lab on a chip *Steven Pollack, PhD* • Digital Pathology *Kyle J. Myers, PhD., Director, Division of Imaging and Applied Mathematics, OSEL*
11:00am-1:00pm	Working lunch/Executive session
1:00-3:00pm	Writing session for committee members

Agenda

Science Board Subcommittee Site Visit to CDRH

October 3-4, 2012

10903 New Hampshire Avenue

Bldg 62, Room 2200 (unless otherwise noted)

Silver Spring, MD 20993

October 3, 2012

6:30-7:30pm		Meet and greet with FDA Staff *Sergio Ristorante Italiano* *8727 Colesville Road* *Silver Spring, MD 20910* *(301) 585-1040*
7:30-9:00pm	Subcommittee	Executive Session *Sergio Ristorante Italiano*

October 4, 2012

7:30am		Arrive at upper lobby of Bldg. 66 W*ill be met by Tynetta Redd* *(301) 796-2530*
8:00-8:30am	Dr. Shuren	CDRH Science programs
8:30-10:30am	Meet with scientists and engineers	Research proposals development and generating support *(3 groups of 2)*
10:30-11:30am	Division Directors	PMAPs, workload distribution, research projects development, budget decisions
11:30am-1:00pm	Working lunch with	Mission, Vision, office priorities,

	OSEL Senior Leadership	decision making, metrics, Center Science Prioritization Process, and OSEL's Science Prioritization Process
1:00-1:30pm		Visit Chemical Contamination Technical Review Committee (TRC) meeting
1:30-2:00pm	Ashley Boam and Donna Lochner	OSEL's role in integrating regulatory science into review decisions
2:00-2:45pm	Subcommittee	Executive Session
2:45-3:00pm	Dr. McMurry-Heath	Wrap up
3:00-3:45pm		Optional follow-up meetings Attend closing of TRC meeting

iii. Interviews

Scientists that Met with the Science Board Subcommittee on October 4, 2012

Name	**Title**	**Primary Expertise**
Jerry Harris	Research Engineer	Ultrasound
Srinidhi Nagaraja	Mechanical Engineer	Failure mechanisms
Peter Goering	Toxicologist	Nanotech,Biomarkers for Tissue Damage
Chistin Welle	Staff Fellow	Neurophysiology
Kim Sapsford	Staff Fellow	Chemistry
Ilko Ilev	Research Physicist	Biophotonics
Berkman Sahiner	Electrical Engineer	Computer-Aided Diagnosis
Lisa Simone	Biomedical Engineer	Manufacturing
Dave Saylor	Materials Engineer	Materials Science
Names of Division Directors Meeting with the Science Board Subcommittee		
Marilyn Lightfoote	Director, DB	Immunology
Larry Grossman	Director, DSFM	Medical Physics
Al Tayor	Director DESE	Electrical Engineering
Dinesh Patwardhan	Director, DCMS	Analytical Chemistry
Kyle Myers	Director, DIAM	Medical Imaging
Victor Krauthamer	Director, DP	Electrophysiology
Names of Senior Office Leadership		
Steve Pollack	Director	Polymer Chemistry
Joel Myklebust	Deputy Director	Biomedical Eng.
Subhas Malghan	Deputy Director	Materials Scientist
Other Office Leadership		
Donna Lochner	Senior Scientific Advisor	OSEL
Ashley Boam	Supervisory Biomedical Eng.	ODE
Maria Chan M.	Supervisory Microbiologist	OIR

Center Leadership

Michelle McMurry-Heath, MD, PHD; Associate Director for Science, Acting Chief Scientist, CDRH
Jeff Shuren, MD, JD; Director, CDRH

5. Findings

a. Core Findings

The subcommittee developed a deep respect for the dedication and accomplishments of the scientists at CDRH. They have intense workloads and the health and wellbeing of patients around the nation are directly impacted by their work. The nature of a report such as this is to emphasize excellence but to also draw attention to areas where strategy or implementation raises questions. Notwithstanding the support just expressed for the science being performed at CDRH, our sub-committee also developed real concerns about how well the research organizations were positioned to meet CDRH's strategic vision and the seemingly inadequate budget to support the direction of CDRH research in the near term and future.

It was made evident to us in writing and in person that science is an integral part of CDRH and great care and time have been extended to support the research arm of CDRH. The overriding sentiments of the review board included universal acknowledgement of: the excellence in science; significant progress, even in the short time that we have initiated and followed up with this Science Board review, with the insight of division leaders into mission and needs of FDA; and the dedication of the staff at every level to perform to the highest standards even with limited resources. At the same time, as noted above, there are issues, many identified in the 2001 and 2007 reviews, and acknowledged by FDA/CDRH leadership in their response to our initial inquiries in this review that remain and have become even more acute. Thus, while we embrace the achievements and good work of the research community at CDRH it is through concern for supporting and maintaining these standards that we offer the following critique.

i The role of research and science in the regulatory process at CDRH

Research is important to the Center's regulatory needs, and integral to the Center's regulatory mission and public health mission. The research portfolio consists of multidisciplinary laboratory research programs in the Office of Science and Engineering Laboratories (OSEL), and regulatory research projects in pre- and post-market offices and epidemiological and statistical research in the Office of Surveillance and Biometrics (OSB). CDRH's regulatory science research program is designed to be proactive, by anticipating regulatory and public health issues, and responsive, by focusing on important and emerging public health and regulatory issues. These issues are for the most part driven by individual laboratories and facilitated by division directors (as described in more detail below).

The regulatory science research is conducted in-house and through collaborations with other Federal organizations, other FDA Centers as well as industry, health care professional organizations, and academia both in the U.S. and abroad. This research provides CDRH with scientific expertise, tools, standards, methodologies, and data to support science-based decision-making and policy development as well as help industry develop, assess, and manufacture new devices and technologies more quickly and efficiently. It was made clear to us that science serves first and foremost to inform reviewers who can now ask for tests based on data and proven methods, and need rather than tradition, whim and fancy – optimizing the review process. Moreover, it was emphasized that science impacts and gets into

the regulatory pathway through feedback from scientists to reviewers, publications, and guidance documents.

ii Current organization of research at CDRH

OSEL and OSB are organized in very different manners. OSEL is a laboratory-based organization with the mission to contribute to the CDRH mission by developing regulatory science tools and providing laboratory data and consultation to active reviews. OSEL serves as the laboratory science nucleus for the Center. Specifically, OSEL supports the scientific basis for regulatory decision-making by developing independent laboratory information for regulatory and other public health activities of CDRH. In addition to providing consultation to Center's regulatory experts, OSEL researchers are involved in mission-oriented science activities including test methods development, risk assessments, forensic investigations, product evaluations, and technology assessment. From a science breadth standpoint, OSEL conducts laboratory research in the areas of physical, life, and engineering sciences as related to the effects of medical devices on human health. CDRH relies upon this work to support its efforts ensuring public safety in areas as varied as medical imaging, medical device software, breast implants, or drug eluting stents.

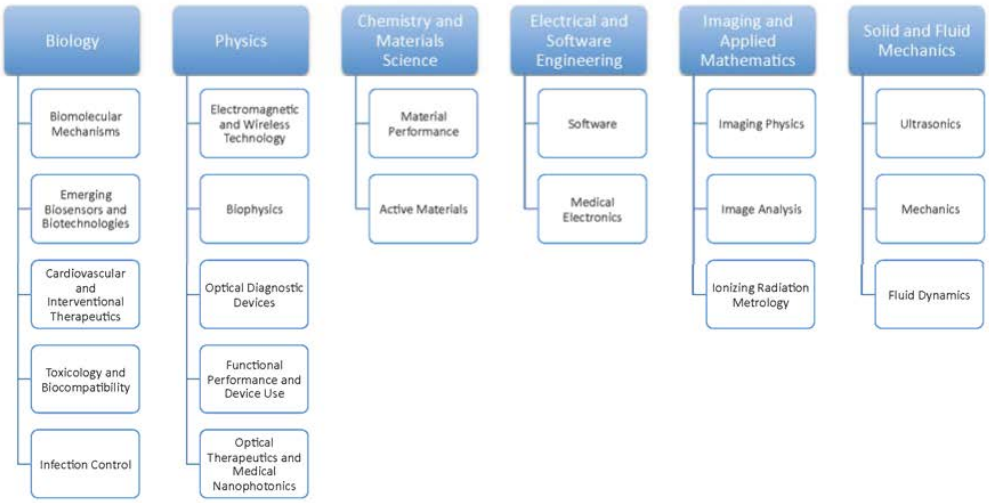
OSEL has six divisions that support 20 laboratories. Laboratories are expected to provide a nucleus of horizontal expertise in a given discipline. Each laboratory is led by a leader who is a senior researcher and has a few principal investigators, post-doctoral fellows, and students. Currently OSEL has some 150 scientific FTEs and up to 60 ORISE fellows (Oakridge Institute for Science and Education) and 30 volunteers.

The OSEL divisions are built around and named for scientific disciplines and with division-affiliated laboratories also based on and named for specific technologies. The laboratory structure is somewhat flexible – laboratories could be created and removed as needs arise and staff can belong to more than one laboratory as their expertise may be needed in multiple disciplines. That said changes in the structure are not common. There are interactions between laboratories in the form of scientific collaborations and resource sharing (staff, equipment, laboratory space, etc.). Projects can be run within a single laboratory or across many, even outside of the governing division. The laboratory framework was instituted to address issues that arose in 2004-2005 with the increasing number of projects and managers, and the need to allow for flexibility to respond to emerging regulatory needs.

The current OSEL structure meshes with the vertical alignment of ODE which is organized by medical specialties (e.g., cardiology, orthopedic, ophthalmology). The benefit of such an organization is that any one OSEL laboratory can then serve and support issues and consults from many divisions in ODE. There are however down-sides to such an organizational structure, including the appearance that OSEL is run like an academic unit with internal focus on science for the sake of driving the fundamentals of the discipline.

Center for Devices and Radiological Health (CDRH)
Office of Science and Engineering Laboratories (OSEL)

Below is the organization structure of OSEL in terms
of six operating divisions and the twenty current laboratories under their respective divisions

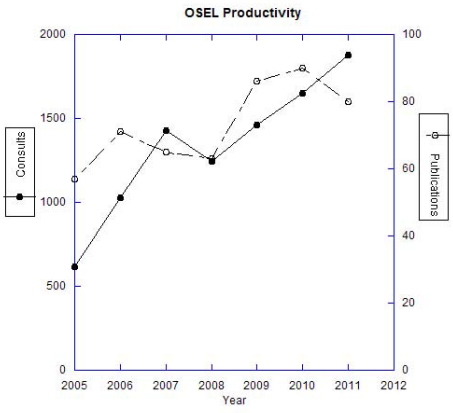


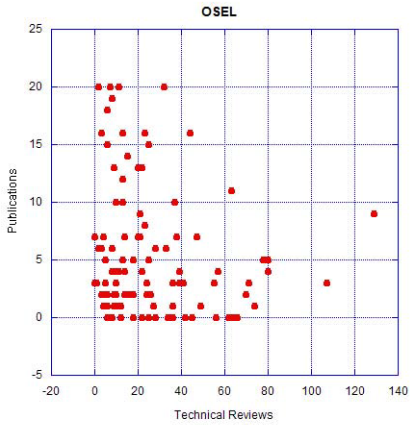
OSEL is currently structured as a traditional research organization with a Director, Deputy Director, Associate Director, and several Assistant Directors. In addition, there are Division Directors, who manage individual laboratories or groups of laboratories. In the past, these Division Directors, in conjunction with OSEL upper management, determined research priorities and budgets for the individual or groups of laboratories. Requests to focus on a particular area of regulatory science or engineering are generated either from within the group or by informal consultation with members of the regulatory staff. There is a formal process for review which determines research priorities for each of the divisions. The review panel is composed of a variety of internal staff members as well as other government experts. While most of the research addresses current regulatory needs, some of the research addresses problems that will arise as new technologies bring new devices before the FDA for review. More recently, the science prioritization process and the allocation of funding have been directed at the Center level under the direction of CDRH's Associate Director for Science and the Center Science Council. As a result, there are substantial differences in budget allocations between the individual divisions. Although the sub-committee did not have the opportunity to see a detailed forward looking budget by laboratory and division, the budget information supported an emerging committee consensus that consolidation of laboratories could be beneficial to achieving the mission.

The subcommittee applauded the efforts of those Division directors (such as Dr. Krauthammer) who sought independent funding to bolster their ability to meet the challenges of their mission. It is clear that all Divisions would benefit from similar strategies.

iii. Demands on staff

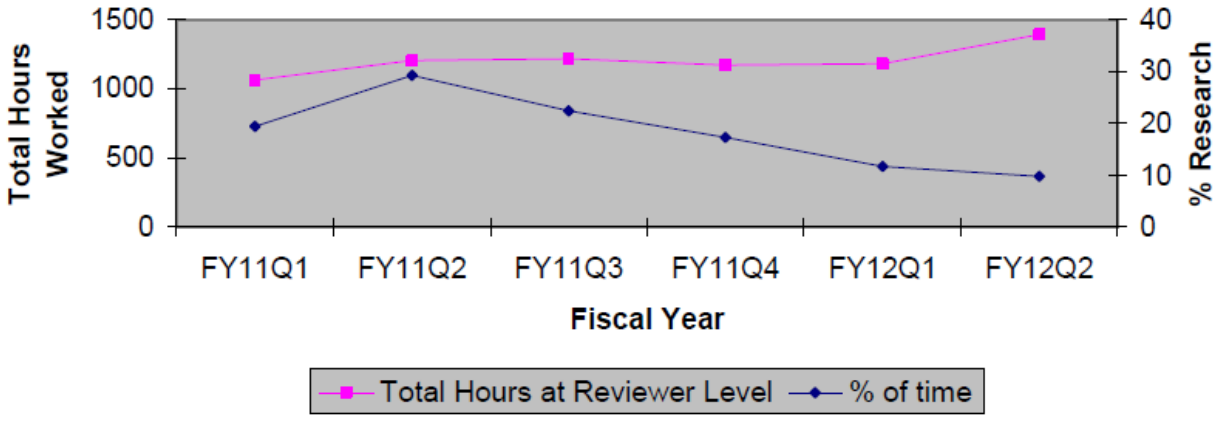
On average, each staff member is an author on approximately 2 publications and completes approximately 14 review consults per year. A large number of staff perform, on average, about 20 consults and produce 5 publications per year. In general, staff that perform a high number of consults, produce fewer publications and staff who produce more publications provide fewer consults. This, however, is not simply a case of staff being more productive when tasked with fewer consults. The workload assignments are based, in part, on staff research productivity.





OSB/ Division of Epidemiology (reproduced from information supplied by CDRH)

Based on the current tracking, in Fiscal Year (FY) 2011, the total percent of time an epidemiology reviewer dedicated to research is estimated as 22%; for FY 2012 the percent of research time is estimated as 20%. The figure below presents the research time per quarter. The data show that although the total hours of work increased, the percent of time the reviewers were able to dedicate to research decreased.



Division of Biostatistics (DBS)

DBS has 55 statisticians, 47 of whom have Ph.D.s – almost all are in statistics or biostatistics. None of the DBS staff positions has a research component. Most of the regulatory research is funded through the Special Projects program. It is estimated that the total FTEs that are devoted to non-premarket

review, which would include research, is between 4 and 5. Some of that effort is on regulatory review that could include research projects, efforts to develop guidance, collaborative research with OSEL scientists and engineers, etc.

iv. Strategic Vision

The sub-committee found that the consideration and articulation of the need and role for past research at CDRH had translated into an effective research vision. That said, we also developed a concern that preparation for sustaining such an effort is not as advanced as needed during a financially perilous time, or at least is not clearly articulated. This concern took a number of forms including, on the one hand, issues related to planning and funding and on the other hand issues relating to clear codification of past public health impact and articulation thereof. It was at times difficult to extract details of how the work at CDRH has saved lives, though it clearly has saved and impacted tens of thousands of Americans without their knowledge. FDA, we believe, has a responsibility to quantify and communicate the impact of its science to the public. The sub-committee also felt that scientists throughout CDRM should be able to explain the mission of the organization and understand how they fit into that complex tapestry of opportunities to excel.

Planning The current fiscal crisis has magnified the issues that confront science at FDA. Two major forces are converging to threaten the viability of the science program at CDRH. First, financial support for FDA science programs has transitioned from stable, "non-competitive" dollars to temporary, "competitive" support. Limiting stable funding to covering primarily the costs of purchasing and maintaining infrastructure, such as equipment, and supporting travel and training, while having staff compete for most of the available CDRH research funds to support new projects, creates pressure on CDRH to assure that the research organizational structure is sufficiently flexible to address emerging technologies and new regulatory science challenges. Second, some scientific research underway at OSEL is diffusing away from regulatory science and is more clearly similar (in some cases identical) to what is being conducted outside of FDA .

Support From the data supplied to the review panel (our analysis is only useful if those data are complete and accurate, <u>which we suspect they may not have been</u>) it seems like OSEL will receive some $11M in 2012, up from $6M in 2009 but down from 2011 levels. Moreover there is an apparent increasing shift in the source of funding and differences in the funding for different directorates. Those funded through the ORISE system are limited to four years in total duration and often people join OSEL in the middle of their ORISE appointment – restricting their tenure at OSEL to the remaining time on their appointment. A confounding challenge is that there is also more work than people (see above re: demands on staff) and that the only way to get more people is to get more work, but added funds cannot support existing people, and existing people do not have the bandwidth to absorb more work. We saw compelling evidence of long processes to distribute funding followed by rushed attempts to spend funds before they disappeared due to annual budget uncertainty. This is not an effective way to perform science and it must be addressed centrally and quickly to the extent possible in light of that fact that the Center's appropriations, contract and purchasing deadlines are outside of CDRH's controls.

Competitiveness A second set of key findings relate to CDRH's ability to excel in the context of what the external community is doing. While the quality of research is high one must acknowledge that there are many reasons for OSEL/CDRH research and only one of them is to add to knowledge in a specific field. FDA scientists have published in excellent journals and metrics of impact are high (average of 36 publications per year, 15 citations per paper, H-index 37) but the major reasons for FDA research are seemingly internal – enhancing the quality of reviews, validating practice, assisting with the generation of standards, anticipating regulatory need and rapid response to acute demand, maintaining the power and potency of individual reviewers amongst others. FDA scientists must compete internally for available FDA research dollars. This approach can help assure that the research conducted by CDRH optimally supports its mission and vision and that CDRH scientists are the appropriate people to do the research. However, when CDRH research efforts are similar to those conducted by or could be conducted by external organizations, it can create competition with external researchers, who have none of the responsibilities of FDA scientists. CDRH should be extremely cautious about thrusting its scientists into head-to-head competition with external researchers who can spend 100% of their time focused on research.

On the one extreme one could argue that FDA should not be performing non-regulatory research that is being performed in universities. At the other extreme, one could argue that this kind of research is often necessary to meet the internal demands of FDA. The challenge then emerges as to how to differentiate between research that meets regulatory need and research that simply advances a field. It seems then that one might classify research into three categories, research that:

(1) should be performed at FDA and if absent would detract from the quality of FDA performance,

(2) can be performed outside of FDA in partnership and collaboration with external scientists, and

(3) advances the field and is going on outside of FDA – and if there were no fiscal or personnel constraints could well be performed by FDA, but would not suffer if FDA were not involved.

Currently it is difficult to discern where in this triptych landscape each program lies. CDRH would be well advised to never start a project that does not clearly fall into the first category, to only pursue projects in the second category in partnership with external groups, if resources are available to the external researchers, and to not pursue projects in the third category. Naturally, there may be rare circumstances in which a compelling public health need requires CDRH to tackle an issue others are able, but for whatever reason, unwilling to address. We suggest that these projects do fall squarely in the remit of the first category above. Importantly, all future external reviews should be facilitated by mapping and substantiating where in this triptych each project and Division portfolio fall.

v. Overview of Findings

FDA and CDRH leadership seem to be aware of most of the concerns we pointed out during our visits. Many of these issues were brought forward in the previous science board reviews in 2001 and 2007, and CDRH made attempts to address these issues and included many of these items in their top

ten recommendations for dealing with emerging issues from this review. In OSEL's self-review they provided a series of striking examples of research that was impactful and that no other group would likely perform. That said, the internal scientific priorities set by the C-SPP Oversight committee are

1 Evaluating New and Emerging Technologies
2. Improving Product Manufacturing and Quality
3. Improving Health of Special Populations
4. Developing Scientific Methodologies for Device Analysis
5. Enhancing Radiation Safety and Radiological Health
6. Evaluating Use Environments, Human Factors, and Wireless, Mobile Medical Devices
7. Infection Control and Protection Against Emerging Infectious Diseases and Terrorism

Naturally, CDRH is continually assessing its Mission, Vision and Values and as a result the list above is a living document that we can only comment on at this point in time.

How the current portfolio of funded projects and laboratory activities at OSEL is in balance with this list is not clearly articulated.

On the resource side of the ledger the supplied list of needs includes desire for:

- Greater support for recruitment and retention of people, and maintenance and improvement of enabling laboratory and scientific resources, in particular for the IT infrastructure.
- Better integration of internal and external strategy and collaboration
  - including harmonizing with scientific needs, across laboratories, with other Federal agencies having common interests, and with universities and non-profit organizations
  - increased awareness of responsiveness to integration of research findings into regulator decision-making
- Enhanced impact
  - facilitating innovation
  - develop metrics for assessing impact
  - globalization
- Need to streamline various Center and Agency level funding opportunities

We would agree with all of the above. Yet, many of these issues were raised in previous review and are still evident and even more acute. The areas of concerns and problems are apparent and appreciated, and the employees willing and capable of doing the work. The leadership has articulated recommendations and foci and while one could argue that some of these are slightly beyond the vision and mission of the FDA, the single greatest challenge is how these recommendations can be implemented. Leadership at all levels should be able to comfortably explain how they would shift their strategy with more or less resources.

b. Organizational Issues

MDIC – Public Private Partnership in Regulatory Sciences A potentially exciting new development for creating needed collaborations in advancing Regulatory Sciences is the establishment of the non-profit Medical Device Innovation Consortium (MDIC). This organization, established in 2012 by the FDA and LifeScience Alley, a biomedical science trade association, is the first public-private partnership dedicated to regulatory science. It is recruiting founding members that represent stakeholder communities with interest in research collaborations and fundraising. The Consortium should become a leading force in advancing science and engineering by breaking down barriers currently impeding the development and use of medical technology.

The Reagan-Udall Foundation, established in 2007, is an example of a private organization dedicated to advancing FDA's mission. The Burroughs Wellcome Fund, a private foundation having an endowment of over $500 million and dedicated to enhancing the biomedical sciences by supporting research and education, has recently announced an initiative to enhance regulatory science. The foundation's "Regulatory Science Awards provide up to $500,000 over five years to academic investigators who are addressing research questions that will lead to innovation in regulatory science, with ultimate translation of those results into improving the regulatory process" (www.bwfund.org). This is a major step since the foundation spends close to $20 million annually, and even a small fraction of this amount is likely to have a major effect on this hardly-existing scientific endeavor. The significant impact that a private organization could have on fostering a needed area of development is The Whitaker Foundation that was instrumental in establishing biomedical engineering as a major area of study at the nation's universities before its closing in 2006.

Regulatory science/engineering is absent from US universities. The field would benefit by establishing it as an academic endeavor that is endorsed by at least some of the country's leading educators. The curriculum would need to be a collaborative responsibility of schools of business, engineering, law, public health (statistics and epidemiology), and medicine. An MS degree in Regulatory Science and Engineering seems to be an appropriate first step, with a curriculum including a common core, complemented by specialization in different aspects of the field depending on the students' background and interest. A consensus meeting, possibly organized by the MDIC, could provide a needed impetus.

An alternative mechanism may be the establishment of a regulatory focus within existing programs. For example, some biomedical engineering MS programs may be interested in establishing curricula that lead to a degree in biomedical engineering, but include regulatory components from complementary areas. Post-graduate courses, potentially developed in consultation with CDRH and/or the MDIC, could attract students who are practicing engineers and scientists whose professional development would benefit by in-depth exposure to regulatory science and practice.

The involvement of industry in partnerships is essential. Such involvement is necessary for achieving industrial "buy-in" for regulatory science and engineering, and for benefiting from industry's insight and

experience. It is impressive that there are already ten industry partners in the organization. Conflicts can be avoided by careful planning. For example, a company paying the tuition for one of its employees at a university seems to be an appropriate mechanism for mutual support.

6. Threats to success

CDRH faces several threats to their success. The review sub-committee believes that CDRH itself has properly assessed two of these: remaining current on technological advancements and the political environment which limits the resources available for scientific growth within CDRH.

However, for CDRH to effectively perform its mission, it must "get ahead of the curve" on technologies to envision those that are likely to enter into the regulatory review domain in the future. It is critical that the leadership of CDRH does not underestimate the nature and scale of the threat. This will require that the agency be active in doing evaluation of the evolving technology landscape. With already high demands on regulatory research staff, this will be difficult to accomplish. Such evaluation could be done either internally or through external contracting. Many possible approaches could be used. It could be done by extensive digestion of the literature, by attending relevant scientific meetings where the future is presented (currently there are very limited funds available for FDA scientists to attend meetings), or through workshops that CDRH could hold, asking key leaders to present their vision of the future in various fields. This would help to define the areas in which new personnel would be required to support the review mission.

Another threat is the size of the scientific staff in CDRH. As noted above, the expectations on staff are very high, and the breadth of science and technologies that must be reviewed is only expanding. Nevertheless, CDRH must respond to these demands within the budgetary constraints. This must be achieved within a fairly inflexible human resources environment, in which it is difficult to recruit new permanent staff. Consideration must be given to how staff scientists can be "retooled" to move into new emerging directions.

The structure of the CDRH science prioritization process and the OSEL laboratories appear to be quite rigid relative to the set of needs that demand agility to accomplish the extensive mission of CDRH regulatory science. There are a number of laboratories organized in a rather traditional disciplinary structure, with interdisciplinary activities that are accomplished by members crossing between laboratories. The Board has insufficient information to determine if this structure is sufficiently flexible to accommodate the review of newly evolving technologies. For example, how and in what areas are decisions made about the scientific expertise of new recruits? Nevertheless, consideration of or allowance for a more cross-cutting topical organization focused on "topical issues" might be considered. Whatever the structure, it is most certainly a threat if the organizational structure is rigid, thereby limiting CDRH's ability to be facile in keeping ahead of new technologies.

7. Recommendations

We recognize the extraordinary efforts and amazing accomplishments of the research arm of CDRH. As advocates for these achievements we must also acknowledge that this is a time of limited and even shrinking resources. The single greatest recommendation we can make is to *more explicitly state the regulatory impact of the spectacular science that is performed and presented **and** foster a better understanding of how FDA research fits in with the scientific community's effort as a whole*. All the presentations to the Science Board and review panel left us in deep appreciation of the span and depth of the work but it was those that specifically mentioned regulatory impact, collaborative integration and science motivated by regulatory need that resonated most. Our concern is that some of the science is being stretched too thin as it simultaneously attempts to meet the expectations of the agency and the precision and rigor of investigative science in general. There is a seeming impending clash between the need to fill this regulatory science role and perceived creep of FDA science in the domain of academia. There are not the resources to enable the latter – not the manpower, culture, time or freedom. For example, restricted travel funds are constraining CDRH science and this issue must be addressed, so that FDA scientists can present their work and discuss science in a scholarly and unconstrained manner. The alignment of FDA structure along a university paradigm sends the wrong message and we would suggest that CDRH take appropriate steps to assure that all of its research programs and research administrative structures address regulatory need.

We find therefore that our specific recommendations are not a far departure from those presented by preceding review boards with the exceptions that these issues are now more acute by virtue of the increasing complexity of the regulatory landscape, the continued growth of knowledge and sophistication of submitted technology and supporting information that must be mastered and the growing fiscal constraints.

Specific recommendations:

Mission and scope:

a. The **primary research mission** of the CDRH should be the fostering of science and engineering with a clear link to regulatory challenges. Every project, laboratory and division should be completely aligned to this mission that no other government agency has.
b. CDRH should establish **quantifiable metrics that characterize the success of research projects in addressing regulatory challenges**. While publications are welcome outcomes, the new metrics should characterize the degree to which the results enhance the timely introduction and continued post-market evaluation of safe and effective medical devices. Quantifiable success metrics should also be developed such that CDRH can measure what negative outcomes have been averted as a result of CDRH regulatory research.
c. In **selecting research projects** for support, CDRH must consider both scientific merit and the prospect of contributing to public health through regulatory science and engineering. The two-

stage scientific prioritization process for selecting research projects is designed to assess both criteria. The process appears cumbersome, and continuing current efforts to improve it is highly encouraged.

d. OSEL, an especially complex office, relies on the two-stage CDRH process for assessing projects to be supported. Since OSEL includes multiple disciplines in laboratories that are diverse and managed in different ways, an internal mechanism for planning and establishing priorities may promote efficiency and the achievement of common goals.

Organization

e. OSEL should consider developing an internal Advisory Board that formally reviews research priorities and provides input on these priorities to the OSEL Director, Deputy Director, Associate Director, and through them to the Division Managers. The overall research priorities of OSEL could also be reviewed by an External Advisory Committee, and input from this Committee could identify high priority areas of investigation. This committee could also identify new areas of investigation not previously identified by internal processes. New committees do, however, add bureaucracy to an already bureaucratic process, so any decision to proceed with this recommendation must be balanced by a strategy that minimizes additional workload or slowing of the pace of decision making.

f. OSEL's structure should be re-assessed to determine the optimal organizational structure to support regulatory science research and regulatory review. One possibility is to consolidate the many laboratories and divisions into a more manageable cluster, focused on different approaches to regulatory science. Each cluster should have critical mass of personnel and balanced funding relative to others.

g. OSB has a simple organizational structure and focused priorities. CDRH should assess whether the successful OSB approach can and should be replicated across the CDRH research program. Naturally, OSB has a smaller research focus and program, but that does not mean that the approach they have taken cannot be scaled to meet the needs of OSEL.

Advocacy, communication and collaboration

h. CDRH should publicize its mission of conducting research related to regulatory challenges. It should develop "success stories" that illustrate how specific research projects actually contributed to faster and/or more effective regulatory action that served public health. Such a list would contribute to demonstrating the necessity of CDRH's research mission, and help the Center to be considered an ally rather than an adversary of the biomedical industry. It would be more compelling than descriptions of ongoing research.

i. OSEL should develop an electronic bulletin board devoted to developments in regulatory science and engineering. This would allow information exchange between regulators in CDRH and staff in OSEL and allow for rapid dissemination of research accomplishments for internal dissemination that would assist regulators. The e-bulletin board would originate in the office of the OSEL Director, who would be responsible for its content. Requests for a subject matter expert on a particular topic could be posted to help identify unrecognized expertise within OSEL,

and research accomplishments that could impact regulatory strategies or clinical trial designs could be presented.

j. CDRH, like other government agencies, is likely to face dwindling financial resources. Enhancing collaboration with outside scientists and their laboratories may mitigate the deleterious effects of scarce resources on regulatory science.

k. CDRH should explore partnering with industry and foundations to establish regulatory science and engineering as an academic endeavor. This would generate knowledge, train needed professionals, and generate recognition of CDRH's mission. The new MDIC could spearhead such an initiative.

l. CDRH should do all it can to help its scientists travel to meetings, interact with outside professional colleagues, and participate in joint research projects. The primary means of doing this might be carefully formulated changes in policy that foster collaborative interactions.

Funding

m. The recently established Medical Device Innovation Consortium is an exciting means to foster public/private interactions. Its development is encouraged. CDRH should help assure that the MDIC has an overall strategy for funding with priorities and understanding as to how to support critical elements in the FDA program.

n. CDRH scientists often respond to many different requests for proposals. These RFPs raise funding possibilities, but they can also be distracting. To the extent possible, RFPs should be coordinated and evaluated by common criteria to minimize their potential distractions.

o. Current efforts to bring talented researchers to CDRH for temporary positions are effective in enhancing scientific interactions. Such efforts should be continued to foster long-term interactions that benefit regulatory science and engineering.

p. The involvement of CDRH scientists in both research and regulatory activities is appropriate, and is strongly encouraged. Being a partner in device evaluation enhances a scientist's understanding of regulatory needs, while being involved in research keeps him or her at the forefront of scientific and technological knowledge. Such complementary nature of duties is attractive to many, and contributes to recruiting and retaining talented and motivated personnel.

q. Efficient information exchange between regulators and researchers might be strengthened by formalized mechanisms such as joint discussions of priorities and needs, and appropriately designed bulletin boards. It is recognized that such mechanisms cannot replace personal interactions, and the time commitment needed for their establishment must to be exceeded by their potential benefit.

r. Balancing the research and regulatory duties of CDRH scientists, especially those of OSEL, is a challenge. The balance needs to take into account both the agency's needs and the scientists' expertise. Achieving an appropriate balance should become a well- articulated goal, understood and cooperatively pursued by both management and staff scientists.

s. CDRH is trying to anticipate emerging regulatory needs that will arise due to scientific and technological advances. This is appropriate and highly encouraged. Such anticipatory activity

should become a major guide while recruiting new scientists and considering support for specific laboratories.

Future Review Processes

Given that the CDRH research program has been reviewed in detail three times in a decade and that each of the reviews while distinct led to similar conclusions, the sub-committee felt that some discussion of codifying the review process may be useful. It is vital that any review begin with a significant amount of time in which leadership at CDRH (Center Director) meet with the committee to discuss his or her mission, vision and strategy. In order to use the sub-committee most effectively the group must understand where leadership is in the complex management challenge of a research program that is so critical to the Nation. This should then be followed by an opportunity for the committee to explore whether CDRH research management "buys in" to the strategy being followed and whether they have put in place tactics that are likely to succeed. The review process will be dependent on CDRH sharing information in a concise and consistent manner and the sub-committee is encouraged that CDRH leadership is developing a set of metrics through which they will be measuring their own performance in research. These metrics should be shared at the onset of future reviews with all relevant data. We recommend that future reviews provide plenty of time for the reviewers to interact with the life-blood of the program: the excellent research staff that innovate and move regulatory science forward. Standardizing the review process and aligning it to ongoing internal reviews will enable reviewers to focus their efforts and ensure that they review single consistent data sets. Review committees that are exposed to the excellence at CDRH will become ambassadors for the program. Finally, prior reviews have not assessed whether the budget of the programs is appropriate for the mission in terms of source and distribution. With the real financial peril that the center faces as a result of Government not understanding the critical nature of the work being done, we recommend that budget alignment should be an appropriate and important area for review.

Conclusions

The FDA Science Board was charged with conducting this review to assess how CDRH's regulatory science portfolio can best anticipate and address emerging medical devices and new public health concerns from currently marketed devices. The subcommittee was also asked to consider the broad scientific disciplines and technologies that CDRH needs to support its regulatory functions and decision making. Specifically, the Board was asked to address the following questions:

- What, if any, changes should CDRH make to its regulatory science research portfolio to best accomplish its public health mission?
- Given the breadth of devices before us and what is anticipated in the future, what should be CDRH's capacity for conducting or collaborating on regulatory science research?
  - Assess any gaps in regulatory science capabilities or expertise.
  - Identify scientific areas where CDRH should make programmatic and resource changes.
  - Identify opportunities for collaboration to better leverage CDRH's regulatory science programs.

- A growing challenge for CDRH is to assure that the Center is optimally prepared to facilitate the development, review, and monitoring of new and emerging medical technologies. What methods, such as horizon scanning and research prioritization, should be used and how could they best be employed to optimally preparing the Center to address new and emerging medical devices?

CDRH research saves lives and prevents medical disasters. CDRH needs the public to understand the critical nature of the research it performs. Projects target already encountered regulatory challenges, as well as anticipated challenges caused by the rapid increase in scientific and technological sophistication. CDRH research serves public health by making the regulatory process faster and more insightful, as well as by contributing to knowledge that will help make future medical devices safer and more effective. We have listed a large number of recommendations that are categorized in a few key areas. Our findings are strikingly similar to prior reviews. Although the landscape of research and the Agency is different today than it was a decade ago, appropriate self-reflection within CDRH will identify past strategies that were successful and others that were not in addressing persistent challenges. Given that reality, and the pending significant constraints on budget it will be vital that CDRH address these issues moving forward.

The subcommittee of the Science Board strongly supports the need for regulatory science and engineering in CDRH, and several of its recommendations advocate making CDRH research even more responsive to regulatory needs. Recommendations are also made to make the research results more visible to professional constituents and the public. Visibility, enhanced by research collaborations and educational efforts, is essential for society's understanding of the need for regulatory science, thereby earning broad-based support for the benefit of all.