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April 7, 2011

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

**RE: Docket No. FDA-2011-N-0063**

To Whom It May Concern:

The Food and Drug Administration's (FDA's) Center for Devices and Radiological Health (CDRH) Medical Device Innovation Initiative report (the report), which was made available for public comment on February 8, 2011, proposes several positive steps for improving the process for developing and reviewing innovative medical devices. However, the agency must ensure that any implementation of these proposals does not adversely impact (a) the safety of patients or human subjects or the public health, or (b) the integrity of the review process for innovative medical devices under the proposed Innovation Pathway.

Our specific comments regarding various sections of the report are as follows:

**A. BACKGROUND – Innovation and Medical Device Development**

(1) Page 5, Figure 1 and page 6, Figure 2 – The presentation of the model of the total product life cycle for a medical device illustrated in these figures suggests that clinical testing is a routine phase in the development of any medical device.

However, as the FDA is aware, most medical devices – and too often, medical devices that present significant risks to patients – do not undergo rigorous clinical testing to reasonably assure their safety and effectiveness before being cleared for marketing by the FDA under the 510(k) pathway.[1] The FDA should ensure that future documents related to the medical device innovation initiative clarify that the total product life cycle, as described in the report, in general is only applicable to a minority medical devices (i.e., those categorized as class III).

(2) Page 6, first paragraph – The report states that "[t]he 510(k) process facilitates access to modified versions of marketed lower-risk products by providing a streamlined review pathway for new devices proven to be 'substantially equivalent' to legally marketed 'predicate' devices."

However, it should be noted that FDA has allowed many devices that have presented significant risk to patients (i.e., not "lower-risk products") to be cleared under the 510(k) pathway.[1]

**B. Proposal 1.1 – Create a Priority Review Program for Pioneering Technologies (the Innovation Pathway)**

(1) Page 8, last paragraph – The report states the following regarding the proposed Innovation Pathway:

> We anticipate that the devices reviewed under this pathway may raise scientific and regulatory questions that are novel, challenging and resource-intensive. While it is critically important to take steps to facilitate the development of transformative innovative devices, we also recognize the importance of meeting our commitments under MDUFA. Therefore, the number of devices that we would be able to accommodate under the Innovation Pathway would depend on available resources. We would closely monitor our resources so that our performance and commitments for the review of other devices are not adversely affected, thus avoiding unintended consequences for devices reviewed under other pathways.

We agree that the proposed Innovation Pathway is likely to require extensive resources in terms of staff time and effort in order to adequately address the complex scientific, regulatory, and patient safety questions that are likely to be raised during the CDRH review process and meet the expedited deadlines that are to be established for such reviews. The FDA must ensure that any shift in resources to the review of devices under the Innovation Pathway does not adversely impact the public health by degrading the adequacy of the review of medical devices under the standard review pathways.

(2) Page 10, first paragraph – The report indicates that devices which are "radically different" in their "underlying technology or manner of use" would be eligible for consideration for the Innovation Pathway.

The FDA should define clearly the parameters for what would be considered a "radically different" medical device.

(3) Pages 10 to 11, **Oversight by the Center Science Council (CSC)** – The report describes the composition and role of the CSC as follows:

> The CSC, a new oversight body currently being developed within CDRH, will be comprised of a cross-disciplinary group of CDRH senior managers and experienced review staff. The CSC would monitor the device development and review processes from the date of acceptance into the Innovation Pathway until the date of regulatory approval (or removal from the Innovation Pathway). As for other submissions, a primary review team would be

assigned; however, under the Innovation Pathway, the primary review team would be assigned earlier in the development process and the team and management would regularly update the CSC on the progress of the submission, unresolved regulatory or scientific challenges, or proposed changes to prior policies or decisions. Early CSC involvement should lead to quicker resolution of difficult scientific issues, early recognition of the need for additional expertise outside the Center, and a reduction in unnecessary delays.

The FDA must ensure that the interactions between the primary review team and the CSC, which will include CDRH senior managers, does not result in inappropriate pressure on the primary review team by the senior managers to recommend approval of an innovative device when the review team has concerns about the safety or effectiveness of a radically different device undergoing review.

(4) Page 11, **Development of an Innovation Pathway Memorandum** – The report describes the purpose of the Innovation Pathway memorandum as follows:

> The memorandum, developed through an interactive assessment process with the sponsor, would describe a proposed roadmap and timeline for device development, clinical assessment, and regulatory review. Delays and uncertainty would be minimized by identifying and addressing difficult, unresolved regulatory science questions (such as appropriate clinical trial endpoints) during the early Innovation Pathway stages.

We support implementation of proposals that would facilitate interactions between the FDA and the sponsor in the early phases of development of an innovative medical device. In particular, the opportunity for FDA to advise the sponsor regarding the design of clinical trials could help ensure that such clinical trials are well-designed from a scientific and ethical standpoint, thus minimizing risks to human subjects and increasing the likelihood that valuable scientific knowledge will be obtained.

(5) Page 11, **Creation of Flexible Clinical Trial Protocols** – The report proposes the following regarding implementation of flexible clinical trial protocols:

> Clinical trial protocols developed through an interactive assessment process would anticipate the need for iterative device testing and redesign, as appropriate, and may employ tools to best leverage available data and minimize delays. For example, multiple stages of clinical evaluation (such as feasibility and pivotal trials) may potentially be performed under a single protocol that allows for a phased-in approach. Iterative clinical trial designs may be employed when treatment effects are uncertain given the novelty of the technology

We note that, depending on how it is implemented, this proposal may not be feasible in the context of the FDA human subject protections regulations regarding institutional review board (IRB) review. For most of the research contemplated under such a protocol (i.e., all planned trials subsequent to the initial pilot or feasibility trial), an IRB, upon receiving the initial submission of the protocol, would not have sufficient information to make the determinations required under the FDA human subject protections regulations at 21 CFR 56.111. For example, given the uncertainty of the treatment effects and novelty of the technology for the types of devices that would be reviewed under the Innovation Pathway, results of the first phase of the flexible clinical trial protocol (e.g., an initial feasibility trial testing the first model of the device) would be directly relevant to assessing the risks and benefits of the second phase of the protocol (e.g., the second feasibility trial testing a modified device) and would need to be provided to the IRB before the IRB could review and consider whether to approve the second phase clinical trial.

The FDA must ensure that this proposal does not create circumstances in which IRBs are pressured to approve flexible clinical trial protocols in their entirety that lack sufficient information for the IRBs to make the determinations required under the FDA human subject protections regulations at 21 CFR 56.111.

**C. Proposal 1.2 - Streamline the *de novo* Pathway**

The report indicates that CDRH intends to issue draft guidance by September 30, 2011 that will, among other things, clarify the criteria for *de novo* process eligibility and, presumably, describe how this review process will be conducted. We look forward to the opportunity to review and comment on this future draft guidance. We previously urged that the United States Congress repeal the statutory provision authorizing the *de novo* process.[1] In the absence of such congressional action, we agree there is a definite need for clear guidance on the criteria for *de novo* process eligibility and how such reviews are conducted by the agency.

**D. Proposal 2 – STRENGTHEN THE U.S. RESEARCH INFRASTRUCTURE AND PROMOTE HIGH-QUALITY REGULATORY SCIENCE**

Page 13, first paragraph – We strongly agree with the FDA's assessment that "having institutions and investigators skilled in good clinical practices can help assure proper clinical trial conduct, thereby also assuring patient protection and data integrity."

**E. Proposal 2.1 – Establish a Voluntary Third-Party Certification Program for U.S. Medical Device Test Centers**

(1) Page 13, first paragraph under the heading for proposal 2.1 – We endorse, in concept, the proposal to develop a program for certifying medical device clinical

trial centers. Such a program, if appropriately implemented, could help ensure that the risks to human subjects enrolled in medical device clinical trials are minimized and that data from such trials is of the highest quality. We reserve further judgment on the merits of this proposal until the FDA releases additional details regarding the entity or entities that will perform the third-party certification, the procedure for obtaining and renewing certification, and the standards for granting certification.

(2) The FDA should consider implementing a similar certification program for U.S. drug clinical trial centers.

**F. Proposal 2.4 – Develop New Science**

Page 15, last paragraph – The report indicates that CDRH plans to explore establishing public-private partnerships as one of several proposed actions to improve regulatory science for medical devices.

To the extent that such partnerships involve FDA staff collaborating with sponsors who will be submitting Premarket Approval (PMA) applications to the FDA, the agency must ensure that there are appropriately safety-proof firewalls between the FDA staff who engage in such collaborative research partnerships and those staff who will be responsible for reviewing and acting on PMA applications submitted by collaborating sponsors.

**G. Proposal 3.2 – CDRH Network of Experts**

Page 17, first paragraph – In the report, CDRH announces its intention to develop a network (or networks) of experts to serve as a resource to assist the agency in better understanding emerging technologies in fields with which the agency's reviewers might not be immediately familiar.

We support the FDA's proposal to seek additional expertise from outside the agency to complement the agency's in-house knowledge and expertise. Because many outside experts commonly will have a variety of financial and professional relationships with sponsors submitting PMA applications to the agency, the FDA must attempt to have an expert network as unencumbered as possible by these conflicts and, in the hopefully rare instances where they exist, to ensure that appropriate procedures are implemented to prohibit such experts from being involved in the review and assessment of any PMA application in which they have a conflict of interest.

Finally, we note that in a January letter to the American public discussing another CDRH initiative to facilitate innovation in medical devices reviewed under the 510(k) pathway, Dr. Jeffrey Shuren, the CDRH Director, stated the following:

> By increasing the predictability, reliability, and efficiency of our regulatory pathways, we can help provide better treatments and diagnostics to patients more quickly, stimulate investment in and development of promising new technologies to meet critical public health needs, and increase the global market position of U.S. medical devices.[2]

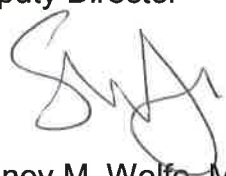
These and other similar comments in Dr. Shuren's letter over-emphasized innovation and the interests of the device industry in comparison to the safety of patients. As the FDA moves forward with its various initiatives to promote medical device innovation, the agency must seek a better balance between promotion of such innovation and the protection of the health and welfare of human subjects and patients.

In summary, we view many of the proposals presented in the report as positive steps, but will need to see more details before rendering a final judgment on many of them. For several proposals, we caution the FDA to take steps to ensure (a) the safety of human subjects and patients, and (b) integrity of the review process under the proposed Innovation Pathway.

Thank you for the opportunity to comment on the report.

Sincerely,

Michael A. Carome, M.D.
Deputy Director



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[1] Hines JZ, Lurie P, Yu E, Wolfe S. Left to their own devices: breakdowns in United States medical device premarket review. PLOS Medicine. 2010; 7:e1000280. http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000280.

[2] Shuren J. A Letter from the center director to the American public. Food and Drug Administration. January 19, 2011. Available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM239451.pdf. Accessed April 7, 2011.