DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

MAR 0 9 2015

The Honorable Lamar Alexander
Chairman
Committee on Health, Education,
Labor and Pensions
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

Thank you for your letter of May 6, 2014, cosigned by three of your colleagues, inquiring about how the Food and Drug Administration (FDA or the Agency) prepares and uses Level 1 draft guidances in carrying out the Agency's regulatory responsibilities.

FDA oversees a myriad of issues related to the regulation of medical products, food, cosmetics, and tobacco. In general, guidance documents describe the Agency's policy and regulatory approach to an issue. They communicate important information on a wide range of regulatory topics, including policies and procedures for inspections and enforcement; content, format, and evaluation of regulated product submissions; and, design, production, manufacturing, and testing of regulated products. Guidances give FDA an opportunity to provide clarity and consistency on issues of importance to a wide variety of stakeholders, including medical professionals, industry, academia, and the public.

Guidance documents generally do not create legally enforceable rights or responsibilities and do not legally bind the public or FDA—importantly, they do represent the Agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence. Because guidance is not binding, affected parties may choose to use an approach other than the one set forth in a guidance document, unless the guidance document is reiterating legal mandates. Any alternative approach must comply with the relevant statutes and regulations. FDA is willing to discuss an alternative approach with affected parties to ensure it complies with the relevant statutes and regulations.

FDA continuously seeks to increase the efficiency and transparency of the guidance development process, and as part of the Agency's Transparency Initiative, we publicly released a comprehensive report in September 2011, setting forth best practices and recommendations that would better facilitate early stakeholder input, efficiency at the Agency level, and the transparency of the process. FDA also created a transparency initiative website, *http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/*, so that the public can track our progress, and an FDA Basics for Industry website,

http://www.fda.gov/ForIndustry/FDABasicsforIndustry/default.htm, to facilitate better communication with the public.

Your letter asks five specific questions about the development and implementation of FDA guidance documents. We have restated your questions below in bold type, followed by our responses.

1. **A list of all Level 1 Draft Guidances, including the date issued, and the timeline with which you plan to withdraw, revise, or finalize each guidance.**

FDA has become increasingly responsive to requests for guidance, without a corresponding increase in staff to handle this responsibility. Guidance documents, both draft and final, can be a challenge to issue. For the vast majority of Level 1 guidance documents, FDA issues a draft guidance for public comment. Each draft guidance is developed by subject matter experts, based on a transparent scientific and/or technical foundation, and undergoes a thorough review and clearance after it is written and before it is made public for comment. This process may sometimes include the Department of Health and Human Services (HHS) and the Office of Information and Regulatory Affairs in the Office of Management and Budget.

In addition to the statutorily mandated guidance, FDA frequently issues guidance where stakeholders have expressed confusion about a topic and when FDA believes additional clarity is needed. When FDA thinks additional stakeholder input is advisable on a topic even before issuing a draft, FDA will open a public docket where all stakeholders are able to provide written input, issue a request for information, hold a public workshop or meeting, or convene an advisory committee meeting. These opportunities for advance input also require a considerable investment of FDA's limited resources.

Once a draft guidance is issued, and the comment period is closed, we review and consider every comment received to determine whether changes are warranted. We may also seek further public input through a public meeting or workshop. The more extensive the comments are, the longer this process takes. For scientific and technical documents, the Agency must also ensure that the final recommendations and supporting references are up to date. In areas of rapid scientific or regulatory development, this need to ensure that the final guidance is current and most useful to the regulated community may prompt us to delay completing a final guidance until our recommendations can stabilize. Once the final document has been written, it undergoes review and clearance, just as the draft did.

Virtually all guidance documents need the specific medical, scientific, or technical expertise of subject matter experts. If the issues covered in a guidance relate to product development, the subject matter experts who are needed to write the guidance also may be handling other priority projects, ranging from key sponsor meetings and review of applications, e.g., NDAs, BLAs, PMAs, ANDAs, NADAs, and ANADAs, many of which are subject to user fee performance goals and some of which represent important medical advances, to developing complex regulations under statutory deadlines. Thus,

the subject matter experts must balance their work on guidance documents with these other priority projects.

We appreciate that over the last several years, you and your colleagues have looked for ways to help us in this endeavor. There may be ways to decrease administrative burdens associated with issuing guidance, where appropriate, and we look forward to engaging with Congress on these types of issues.

We are attaching, as Appendix 1, a list of draft guidances that had been outstanding for 12 months or more as of December 2014, from eight FDA Centers and Offices:

- Center for Drug Evaluation and Research (CDER)
- Center for Devices and Radiological Health (CDRH)
- Center for Biologics Evaluation and Research (CBER)
- Center for Food Safety and Applied Nutrition (CFSAN)
- Center for Veterinary Medicine (CVM)
- Center for Tobacco Products (CTP)
- Office of Special Medical Programs (OSMP)
- Office of Regulatory Affairs (ORA)

The Centers and Offices are continuing to work on their plans for which guidances will be withdrawn, reissued, or finalized. We will provide the additional information as soon as possible.

Two categories of draft guidance documents are not included in this compilation; as we reviewed our draft guidances, we determined it was not appropriate to include them.

The first category is guidance documents produced through the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). These organizations bring together regulatory authorities from Europe, Japan, and the United States, and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration to achieve greater harmonization. ICH and VICH have adopted a multi-step process for developing guidelines that FDA then also adopts as guidance. Because the ICH and VICH process is not driven by FDA, and the FDA process follows after the ICH/VICH process is completed, we have not included these draft guidance documents in Appendix 1.[1]

The second category is CDER product and/or indication-specific recommendations issued as draft guidance. The vast bulk of these are generic drug bioequivalence guidance documents. These documents provide potential sponsors with information from

[1] *http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM271036.pdf*

FDA on drug development for specific products and are developed by FDA subject matter experts to make public and transparent the Agency's thinking, rather than only sharing the information with individual applicants. Drug development science also unfolds over time as research is done and new approaches are identified by FDA or potential applicants. Thus, these kinds of documents need to be periodically updated.

For these product and/or indication-specific guidances, it would be extremely burdensome for FDA to undertake to re-issue and/or finalize while maintaining our current drug user fee commitments. However, we know from our experience and from hearing from our stakeholders that these documents are extremely useful, and we are reluctant to simply withdraw them. We do not believe that leaving these documents in place will undercut communication. We encourage potential applicants to meet with us early to discuss their product development plans and we share updated information in these meetings. Thus, we believe that making these documents available in the public domain will inform product development discussions with FDA.

Senior Agency leaders are engaged in a discussion about how we can do a better job finalizing draft guidances in a more timely fashion. Without new resources, in order to ensure that guidances can be finalized in a timely manner, FDA will need to issue fewer discretionary guidance documents. This may disappoint stakeholders, as they often tell us that they find draft guidances provide useful information, even before they are finalized. In light of this concern, the Agency may modify actions and target dates based on stakeholder feedback.

2. **An update on Agency-wide activities to implement the "best practices" to make the finalization of guidance more efficient and expeditious, as discussed in the 2011 report *Food and Drug Administration Report on Good Guidance Practices: Improving Efficiency and Transparency.***

The December 2011 *Food and Drug Administration Report on Good Guidance Practices: Improving Efficiency and Transparency* (Report) included a number of recommendations, both for practices within each Center/Office related to the development of guidances and Agency-wide practices. Since publication of the Report, work has progressed on a number of the FDA-wide initiatives in response to the Report's recommendations.

Tracking Guidance – *(Chapter 2/recommendation 2: "Each Center/Office should implement work planning and tracking strategies to ensure that affected staff are fully aware of established time-frames. These strategies may include: Better, more integrated tracking systems (e.g., the Agency-wide tracking system that RPMS is enhancing and updating)"*

In an effort to help better track Agency development of regulations and guidances, in early 2011, FDA embarked on a redesign of the outdated and outmoded Agency-wide tracking system. Redesign of the current *Federal Register* Document Tracking System (FRDTS) involved a significant commitment of resources and time. The system had to

accommodate all of the various Centers/Offices using the system, thus requiring modifications to the different required fields to ensure all needs were addressed. After a testing phase, the new FRDTS system was formally rolled out on August 25, 2014.

Streamlining the Review/Clearance Process for Guidance: *(Chapter 4/recommendation 3: Streamlining the review/clearance processes in a number of ways: Identifying the appropriate reviewers prior to initiating clearance to avoid requesting clearance unnecessarily from certain individuals or offices.)*

The Office of Policy has initiated practices to ensure that earlier in the review process, the Center/Offices identify which guidances will require substantive review and clearance by the Office of Policy. This helps streamline the review process timeline and better manages expectations of when the guidance document will leave FDA for further external review. Once the review process is completed, a "notice of availability" is published in the *Federal Register*.

Centralized Webpage for Guidances: *(Chapter 5/Recommendation 7: FDA should continue to -- Provide a centralized webpage that links to each Center/Office's guidance list on FDA Basics for Industry, and update it as needed, and -- Build a centralized webpage that links to a list of guidances that have been withdrawn by the Centers/Offices, and once it has been completed, update it as needed.)*

Since the 2011 Report was issued, the Office of the Commissioner, including the Office of Policy, has been actively engaged in building and implementing a centralized webpage that links to a list of guidances, including links to those that have been withdrawn by the Centers/Offices. Once it has been completed, it will be updated as needed. This effort, similar to the redesign of the FRDTS system, has required a significant amount of resources and time. Guidances currently on the web are not all located in one place. In order to develop one website, with search capability across all of the Agency guidances, the data underlying the guidances must all be similar and use the same terms and metadata. IT staff is busily working with policy staff to identify the needed IT capabilities and new terms required to ensure the merging of all of the guidances. Given the number of existing guidances, revising the already entered metadata will take time. For new guidances, using common metadata terms will be implemented, going forward. There is current beta testing, with respect to a new webpage, metadata, and weblinks. Significant issues are being identified and worked on in a systematic manner to ensure the best possible system for the public and the Agency.

Several Centers utilize templates for guidance documents, which are instrumental in organizing guidance content and presenting material in a logical sequence.

With respect to the implementation by the Centers and Offices of other recommendations in the Report, the following examples identify some of those efforts:

CDRH:

- CDRH has adopted a Standard Operating Procedure (SOP) on Guidance Development (effective July 31, 2011; available at *http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM266073.pdf*) that sets time frames for collecting the public comments received on a draft guidance and distributing those comments to members of a guidance Working Group for analysis. The SOP also sets time frames for analyzing comments and for drafting the final version of the guidance; however, there is some flexibility in those time frames, depending on the number and complexity of comments received.

- CDRH's guidance webpage lists Center guidances by Office (e.g., guidances issued by the Office of Device Evaluation, guidances issued by the Office of Surveillance and Biometrics, etc.). Within each such list, draft guidances are clearly identified as "draft" in the title of each such guidance. See "Guidance Documents (Medical Devices and Radiation-Emitting Products)," available at *http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm*. In addition, CDRH's guidance webpage includes a prominent search feature, so that a simple search for the term "draft" will result in a listing of draft guidance documents.

  On June 5, 2014, CDRH held a Public Workshop on Guidance Development and Prioritization at which stakeholders and CDRH staff explored ideas to expedite the finalization of draft guidances. As a result, CDRH announced in the *Federal* Register on January 9, 2015 (80 FR 1424), the Center's commitment to performance goals for current and future draft guidances. For draft guidance documents issued after October 1, 2014, CDRH will finalize, withdraw, reopen the comment period, or issue another draft guidance on the topic for 80 percent of the documents within three years of the close of the comment period. For draft guidances for which CDRH does not take action within the initial three years, CDRH will finalize, withdraw, reopen the comment period, or issue another draft guidance on the topic within five years. In addition, in FY 2015, CDRH will finalize, withdraw, or reopen the comment period for 50 percent of existing draft guidances issued prior to October 1, 2009. CDRH is currently developing plans for implementing additional ideas developed at that Public Workshop. For more information regarding the Workshop, see *http://www.fda.gov/medicaldevices/newsevents/workshopsconferences/ucm394821.htm*. Also, CDRH announced an approach for periodic review of final guidances to update them, if warranted.

CDER

- On August 7, 2013, CDER announced in the *Federal Register* (78 FR 48175) an initiative to review draft guidance documents issued before 2010 to

determine their status and to decide whether those guidances should be withdrawn, revised, or finalized with only minor changes. Under that initiative, CDER withdrew 23 guidances that were considered out of date, and thus, of little use to the pharmaceutical industry. Independent of that initiative, CDER actively revises and withdraws guidances, and such updated information is posted on a regular basis on its guidance webpage. The listed information provides the type of guidance and date of issuance/withdrawal.

- Currently, CDER is in the process of implementing project management software that will facilitate the development of guidances by tracking the various tasks required. Implementation of the software will allow CDER to identify the areas where guidance development takes the longest, so that the Center can determine corrective measures for improvement. This is an enhancement from the previous software used, which didn't include specific tasks for guidance development.

CTP

- CTP developed SOPs for developing guidance documents, which are designed to ensure the development of high-quality documents in an efficient manner. The Center adheres closely to these SOPs. CTP begins work to finalize a draft guidance when it has reviewed all the comments received and has resolved any outstanding issues. The Center maintains a current list of its guidances on its website. When a guidance document is finalized, the draft guidance is taken down from the list and archived.

CVM

- CVM has SOPs for developing guidance documents, along with template guidance initiation work sheets and work plans. These are designed to ensure efficient development of high quality draft and final guidance documents. In addition, the Center is initiating a formal program of periodic review of pending draft guidances to ensure timely finalization of such guidances.

OSMP

- OSMP has created SOPs to ensure that consistent processes are implemented across OSMP offices for developing, issuing and withdrawing guidance documents.

3. **Have you implemented the President's Council of Advisors on Science and Technology recommendation to rely more on the biomedical community in help developing and revising guidances, and if so, could you provide examples of specific guidances?**

The following examples illustrate how various Centers work with the biomedical community in the development and revision of guidances.

CDER: has relied on the biomedical community for help in developing and revising guidances. CDER has collaborated with the International Conference for Harmonization (ICH) for many years in developing guidances specific to clarifying the requirements for ICH. In addition to ICH, CDER has relied on input from patient-focused groups and other members of industry, from direct collaboration or public consultation through public workshops or part 15 hearings. Some examples include:

- ANDA Stability Testing of Drug Substances and Products; Final Guidance – developed with the assistance of the Generic Pharmaceutical Association (GPhA) (June 2013).

- Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets; Final Guidance – developed based on feedback obtained at a public workshop to identify epidemiology best practices (May 2013).

- Safety Considerations for Product Design to Minimize Medication Errors; Draft Guidance – developed based on feedback obtained at a public workshop to input how to minimize medication errors (December 2012).

- Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products: Content and Format; Draft Guidance – developed using feedback from the Brookings Institution expert workshop on prescribing information for health care professionals (September 2013).

- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product; Draft Guidance – developed based on feedback received from two public hearings (February 2012).

- Dosage Delivery Devices for Orally Ingested OTC Liquid Drugs; Final Guidance – development was driven by both a *JAMA* article and work done by CDC as part of the PROTECT Initiative (collaboration with public health agencies, private sector companies, professional organizations, consumer/patient advocates and academic experts to develop strategies to keep children safe from unintentional medication overdoses) (May 2011).

- Pulmonary Tuberculosis: Developing Drugs for Treatment; Draft Guidance – developed based on input from the Critical Path Institute's Critical Path To TB Drug Regimens (CPTR) (November 2013).

- Irritable Bowel Syndrome: Clinical Evaluation of Drugs for Treatment; Final Guidance – developed based on input from the International Foundation for Functional Gastrointestinal Disorders and Rome Foundation (May 2012).

- Duchenne Muscular Dystrophy: Developing Drugs for Treatment; Draft Guidance under development based on submission to FDA of an independent guidance drafted by a consortium of stakeholders organized by Parent Project Muscular Dystrophy, including patients, parents, and caregivers, clinicians, scientific experts, and industry representatives (June 25, 2014). The guidance submitted by the consortium was made available by FDA through a *Federal Register* notice seeking public comment (September 4, 2014), and the public comments received in response to the *Federal Register* notice are also being carefully considered by FDA for incorporation into the guidance

CBER: regularly interacts with industry and standards-setting organizations. Through these meetings, industry and others inform CBER of topics of interest for guidance development. In addition, as appropriate, CBER may choose to seek public input and advice through various public meetings to learn more about the issues presented in a draft guidance or to consider new scientific information as it becomes available. For example:

- In July 2013, CBER published a draft guidance document entitled "Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products." By issuing this draft guidance, the Office of Cellular, Tissue and Gene Therapies (OCTGT) was endeavoring to provide those members of the biomedical community that are interested in developing cellular and gene therapy products with information and perspective that will improve the early development of these products and facilitate interaction with OCTGT.

- In February 2014, CBER presented the draft guidance document for discussion at a Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) meeting. CTGTAC reviews and evaluates available data relating to the safety, effectiveness, and appropriate use of human cells, human tissues, gene transfer therapies, and xenotransplantation products, which are intended for transplantation, implantation, infusion, and transfer in the prevention and treatment of a broad spectrum of human diseases and in the reconstruction, repair, or replacement of tissues for various conditions. FDA will consider the input from CTGTAC and the comments to the docket into account before issuing a final guidance.

CBER maintains a website with a list of new topics for guidance documents or revisions to existing guidance documents that the Center is intending to publish during the coming year.

CDRH: actively engages stakeholders, including the biomedical community, in guidance development activities. Examples include:

- On June 5, 2014, CDRH held an all-day Guidance Development and Prioritization Public Workshop,[2] which was attended by many participants representing the medical device stakeholder community. Topics discussed included CDRH's guidance

[2] *http://www.fda.gov/medicaldevices/newsevents/workshopsconferences/ucm394821.htm.*

development process; guidance development best practices for FDA, CDRH, and CDRH stakeholders; and CDRH guidance priorities and priority development.

- CDRH's *Network of Experts* is a vetted network of outside scientists, clinicians, and engineers who provide CDRH staff with rapid access to scientific, engineering, and medical expertise, when it is needed to supplement existing knowledge and expertise within the Center. This program is designed to broaden CDRH exposure to scientific viewpoints, but not to provide external advice or opinions on policy.

- The Center maintains a dedicated website with a list of guidance documents that CDRH fully intends to publish (the "A-list") and a list of guidance documents that they intend to publish as resources permit (the "B-list"). The Center has established a process allowing stakeholders a meaningful opportunity to provide comments and/or propose draft language for proposed guidance topics; to provide suggestions for new or different guidance documents; and to comment on the relative priority of topics for guidance. CDRH has opened a public docket (FDA-2012-N-1021) inviting interested persons to submit comments on any or all of the guidance documents on the list. Comments may include draft language on the proposed topics, suggestions for new or different guidance documents, and/or the relative priority of guidance documents.

CVM: Examples of interaction with the biomedical community include:

- Participation by CVM in the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). VICH brings together the regulatory authorities of Europe, Japan, and the United States, and experts from the pharmaceutical industry in the three regions, to discuss scientific and technical aspects of veterinary product regulation. The VICH recommends ways to achieve greater harmonization in the interpretation and application of technical guidances and requirements for product regulation to reduce or obviate duplication of testing carried out during the research and development of new animal drugs.

The VICH guidelines on the technical requirements for marketing authorization applications for veterinary medicinal products are developed via a 9-step process by expert working groups comprising experts from the different VICH members, from the observers and from VICH Outreach Forum countries on the topics identified by the VICH Steering Committee in a consultative process. The Steering Committee is the body within VICH that is empowered to make decisions such as selecting topics, releasing draft guidelines for consultation, and adopting final guidelines for implementation in the three regions. The VICH Steering Committee currently meets approximately every nine months. The location of meetings, which normally last two days, alternates between Japan, the European Union, and the United States. (Please visit *http://www.vichsec.org/* for more information about VICH.)

- CVM maintains a dedicated website with a list of possible new topics for guidance documents or revisions to existing guidance documents that the Center is

intending to publish during the coming year. The list provides contacts for the public to submit comments on these guidance topics.

4. For the guidances still in draft form, how do you ensure your staff does not follow the guidance in the absence of any other policy or final guidance?

The primary goal of guidance is to share broadly FDA's current thinking on a specific issue or set of issues. FDA also issues draft guidance documents so stakeholders can comment on the Agency's thinking before it is finalized into final guidance. Every FDA program must also apply FDA's statutes and regulations daily to a multitude of situations, even when there is no guidance. Good Guidance Practices (CGP) recognize this. Under GGP, if FDA has issued final guidance that addresses an issue, then staff follows that guidance unless they obtain supervisory concurrence to do otherwise. If there is no guidance on the issue or a draft guidance, then staff interprets and applies the statute and regulations to the specific issue in front of them. We understand that it may look like FDA staff are relying on a draft guidance when staff reach the same result as the one in the draft; this is not as a result of applying the draft guidance; it is as a result of applying the statute and regulations. A draft guidance reflects FDA current thinking, and thus also usually reflects its current interpretation of the statute and regulations.

FDA takes its responsibilities regarding the proper development and use of Agency guidance documents seriously. In order to ensure that in these circumstances a practice or policy described in a draft guidance is not treated as a final guidance before the final guidance is published, FDA takes several measures (as noted below) regarding draft guidances.

For the draft guidance documents themselves, FDA clearly marks them as draft. The phrase "Draft Guidance" is clearly displayed in large font and in a prominent position on the cover page, along with the statement, "This guidance document is being distributed for comment purposes only." In addition, the header of each page of a draft guidance displays the phrase "Draft — Not for Implementation." Moreover, all FDA draft guidance documents include a statement in a prominent box immediately preceding the actual text of the guidance that "This draft guidance, when finalized, will represent the Food and Drug Administration's current thinking on this topic."

The Agency is committed to providing initial and ongoing training for employees about how to develop and use guidance documents. FDA provides employees with guidance training utilizing a variety of approaches, formats, and communication media to maximize the timely, widespread distribution of current guidance information. If a member of the public has a concern regarding an FDA staff member's adherence to a draft guidance, the person can raise this with the employee's supervisor, as well as with others in FDA, as explained in 21 CFR 10.115(o).

5. What is the average amount of time in calendar days that the FDA has taken to finalize draft guidances in the last five years? What is the range?

As mentioned, FDA continuously seeks to increase the efficiency of the guidance development process and is working to improve the speed at which it finalizes guidance documents.

The numbers provided in the chart below reflect final guidance documents published from June 1, 2009, through June 30, 2014.[3]

Title: Number of days it takes for draft guidances to be finalized

Center	Minimum days	Maximum days	Median days
CBER	261	1975	743
CDER	194	5405[4]	710
CDRH	142	2722	797
CFSAN	90	1502	454
CTP	22	1253	237
CVM	238	1527	477
OFVM	80	771	425
OSMP	280	2124	687

If you have further questions, please let us know. The same letter has been sent to your cosigners.

Sincerely,

for Thomas A. Kraus
Associate Commissioner for Legislation

[3] As with question 1, guidances related to ICH or VICH, and product or indication-specific guidances, have been omitted. The data reflect differences between the dates draft guidances were published and the dates the corresponding final guidances were published.

[4] The guidance *Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations* was originally developed by CBER, and during a reorganization, the responsible CBER office became a part of CDER. There was subsequent change in personnel, and guidance finalization lost traction. During the initiative to identify guidances published prior to 2010 we realized that the guidance was still in draft. CDER finalized the guidance on April 22, 2014.