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.

APPENDIX 1: Food and Drug Administration Draft Guidance Documents Published Before 12/31/2013 that are Still Pending

Center/ Office	Draft Guidance	Publication Date
CBER	Draft Guidance for Industry: Platelet Testing and Evaluation of Platelet Substitute Products	5/20/1999
CBER	Draft Guidance for Industry: Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Intimate Contacts	2/11/2002
CBER	Draft Guidance for Industry: Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics as Red Blood Cell Substitutes	10/28/2004
CBER	Draft Guidance for Industry: Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products	2/11/2008
CBER	Draft Guidance for Industry: Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Whole Blood and Blood Components for Transfusion and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)	3/26/2009
CBER	Draft Guidance for Industry: Amendment to Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products	6/11/2012
CBER	Draft Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products	7/2/2013
CBER	Draft Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Human Cells, Tissues, and Cellular and Tissue Based Products	10/24/2013
CBER	Draft Guidance for Industry: Use of Pre-amendments Devices and FDA-cleared Diagnostic Tests to Test Donors of Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps) for Infection with Treponema Pallidum	11/5/2013
CBER	Draft Guidance for Industry: Recommendations for Premarket Notification (510(k)) Submissions for Nucleic Acid-Based Human Leukocyte Antigen (HLA) Test Kits Used for Transfusion and Transplantation	11/20/2013
CDER	Submitting Debarment Certification Statements	10/2/1998
CDER	Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products	11/19/1998
CDER	Accelerated Approval Products —Submission of Promotional Materials	3/26/1999
CDER	Applications Covered by Section 505(b)(2)	12/8/1999
CDER	Pediatric Oncology Studies In Response to a Written Request	6/21/2000
CDER	Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications	10/26/2000
CDER	Providing Regulatory Submissions in Electronic Format - Prescription Drug Advertising and Promotional Labeling	1/1/2001
CDER	Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines	3/12/2001
CDER	Statistical Aspects of the Design, Analysis, and Interpretation of Chronic	5/8/2001

Center/ Office	Draft Guidance	Publication Date
	Rodent Carcinogenicity Studies of Pharmaceuticals	
CDER	Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation	8/21/2002
CDER	Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals	9/11/2002
CDER	Comparability Protocols -- Chemistry, Manufacturing, and Controls Information	2/25/2003
CDER	Current Good Manufacturing Practice for Medical Gases	5/6/2003
CDER	Comparability Protocols - Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information	9/5/2003
CDER	Providing Regulatory Submissions in Electronic Format - General Considerations	10/1/2003
CDER	Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions-Draft Guidance	1/1/2004
CDER	"Help-Seeking" and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms	1/26/2004
CDER	Labeling for Combined Oral Contraceptives	3/5/2004
CDER	Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling	11/1/2004
CDER	Clinical Lactation Studies--Study Design, Data Analysis, and Recommendations for Labeling	2/8/2005
CDER	Expiration Dating of Unit-Dose Repackaged Drugs: Compliance Policy Guide	5/31/2005
CDER	How to Comply with the Pediatric Research Equity Act	9/7/2005
CDER	Public Availability of Labeling Changes in "Changes Being Effected" Supplements	9/20/2006
CDER	Target Product Profile -- A Strategic Development Process Tool	3/30/2007
CDER	Pharmacogenomic Data Submissions — Companion Guidance	8/28/2007
CDER	Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route	3/7/2008
CDER	Integrated Summary of Effectiveness	8/28/2008
CDER	Tropical Disease Priority Review Vouchers	10/20/2008
CDER	Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches	12/16/2008
CDER	Presenting Risk Information in Prescription Drug and Medical Device Promotion	5/27/2009
CDER	Microbiological Data for Systemic Antibacterial Drug Products — Development, Analysis, and Presentation	9/17/2009
CDER	Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications	10/1/2009
CDER	SPL Standard for Content of Labeling Technical Qs & As	10/1/2009
CDER	Assay Development for Immunogenicity Testing of Therapeutic Proteins	12/4/2009
CDER	Assessment of Abuse Potential of Drugs	1/26/2010
CDER	Adaptive Design Clinical Trials for Drugs and Biologics	2/26/2010
CDER	Non-Inferiority Clinical Trials	3/1/2010

Center/ Office	Draft Guidance	Publication Date
CDER	Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling	3/22/2010
CDER	Enforcement Policy -- OTC Sunscreen Drug Products Marketed Without an Approved Application	6/14/2011
CDER	Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices	12/27/2011
CDER	Use of Histology in Biomarker Qualification Studies	12/29/2011
CDER	Guidance for Industry on Biosimilars: Q & As Regarding Implementation of the BPCI Act of 2009	2/9/2012
CDER	Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product	2/9/2012
CDER	Scientific Considerations in Demonstrating Biosimilarity to a Reference Product	2/9/2012
CDER	Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations	2/9/2012
CDER	Drug Interaction Studies--Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations	2/17/2012
CDER	Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage	2/21/2012
CDER	Classifying Significant Post-marketing Drug Safety Issues	3/8/2012
CDER	Drug Safety Information -- FDA's Communication to the Public	3/8/2012
CDER	Direct-to-Consumer Television Advertisements -- FDAAA DTC Television Ad Pre-Dissemination Review Program	3/12/2012
CDER	Guidance for Industry: Organ-Specific Warnings: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use — Labeling for Products That Contain Acetaminophen	7/3/2012
CDER	Suicidal Ideation and Behavior: Prospective Assessment of Occurrance in Clinical Trials	8/14/2012
CDER	Guidance for Industry: Self-Identification of Generic Drug Facilities, Sites, and Organizations	8/22/2012
CDER	Guidance for Industry: Initial Completeness Assessments for Type II API DMFs Under GDUFA	10/1/2012
CDER	Safety Considerations for Product Design to Minimize Medication Errors	12/12/2012
CDER	Certification Process of Designated Medical Gases	12/13/2012
CDER	Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products	12/14/2012
CDER	Guidance for Industry: Providing Submissions in Electronic Format -- Summary Level Clinical Site Data for CDER	12/18/2012
CDER	Abuse-Deterrent Opioids-Evaluation and Labeling	1/9/2013
CDER	Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice	2/27/2013
CDER	Formal Dispute Resolution: Appeals Above the Division Level—Draft	3/12/2013
CDER	Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants	3/29/2013
CDER	Providing Postmarket Periodic Safety Reports in the ICH E2C(R2) Format	4/5/2013

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	(Periodic Benefit-Risk Evaluation Report)	
CDER	Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors	4/23/2013
CDER	Charging for Investigational Drugs Under an IND — Qs & As	5/8/2013
CDER	Expanded Access to Investigational Drugs for Treatment Use — Qs & As	5/8/2013
CDER	Contract Manufacturing Arrangements for Drugs: Quality Agreements	5/24/2013
CDER	Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases	7/1/2013
CDER	Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans	7/12/2013
CDER	Pre-Launch Activities Importation Requests (PLAIR)	7/24/2013
CDER	Generic Drug User Fee Amendments of 2012: Questions and Answers (Revision 1)	9/10/2013
CDER	Bioanalytical Method Validation [Revised Final]	9/12/2013
CDER	Endocrine Disruption Potential of Drugs: Nonclinical Evaluation	9/19/2013
CDER	Product Name Placement, Size, and Prominence in Advertising and Promotional Labeling	11/18/2013
CDER	Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application	12/4/2013
CDER	Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules	12/9/2013
CDER	Naming of Drug Products Containing Salt Drug Substances	12/24/2013
CDRH	Assessing the Safety and Effectiveness of Home-Use In Vitro Diagnostic Devices: Draft Points to Consider Regarding Labeling and Premarket Submissions	10/5/1988
CDRH	510(k) Submission of Lymphocyte Immunophenotyping IVDs Using Monoclonal Antibodies	9/26/1991
CDRH	510(k) Submission of Immunoglobulins A, G, M, D, and E Immunoglobulin System In Vitro Devices	9/1/1992
CDRH	Draft Guidance for Preparation of PMA Applications for Testicular Prostheses	3/16/1993
CDRH	Emergency Resuscitator Guidance	4/14/1993
CDRH	510(k) Submission Requirements for Peak Flow Meters	1/3/1994
CDRH	Reviewer Guidance on Face Masks and Shield for CPR	3/16/1994
CDRH	Reviewer Guidance for Ventilators	7/1/1995
CDRH	Testing MR Interaction with Aneurysm Clips	5/22/1996
CDRH	Review Criteria Assessment of Portable Blood Glucose Monitoring In Vitro Diagnostic Devices Using Glucose Oxidase, Dehydrogenase or Hexokinase Methodology	2/28/1997
CDRH	Premarket Notification [510(k)] Submissions for Medical Sterilization Packaging Systems in Health Care Facilities	3/7/2002
CDRH	Premarket Submissions and Labeling Recommendations for Drugs of Abuse Screening Tests	12/2/2003
CDRH	Class II Special Controls Guidance Document: Tinnitus Masker Devices	11/8/2005
CDRH	Class II Special Controls Guidance Document: Absorbable Hemostatic Device	10/31/2006

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CDRH	Premarket Notification [510(k)] Submissions for Medical Devices that Include Antimicrobial Agents	7/19/2007
CDRH	In Vitro Diagnostic Multivariate Index Assays	7/26/2007
CDRH	Coronary Drug-Eluting Stents: Nonclinical and Clinical Studies Companion Document	3/26/2008
CDRH	Coronary Drug-Eluting Stents: Nonclinical and Clinical Studies	3/26/2008
CDRH	Submission and Review of Sterility Information in Premarket Notification [510(k)] Submissions for Devices Labeled as Sterile	12/12/2008
CDRH	Class II Special Controls Guidance Document: Tissue Expander	12/22/2008
CDRH	Heart Valves: Investigational Device Exemption and Premarket Approval Applications	1/20/2010
CDRH	Class II Special Controls Guidance Document: Electroconductive Media	4/5/2010
CDRH	Class II Special Controls Guidance Document: Cutaneous Electrode	4/5/2010
CDRH	Class II Special Controls Guidance Document: Transcutaneous Electrical Nerve Stimulator for Pain Relief	4/5/2010
CDRH	Class II Special Controls Guidance Document: Transcutaneous Electrical Nerve Stimulator with Limited Output for Pain Relief	4/5/2010
CDRH	Class II Special Controls Guidance Document: Transcutaneous Electrical Stimulator for Aesthetic Purposes	4/5/2010
CDRH	Class II Special Controls Guidance Document: Transcutaneous Electrical Stimulator with Limited Output for Aesthetic Purposes	4/5/2010
CDRH	Class II Special Controls Guidance Document: Powered Muscle Stimulator for Rehabilitation	4/5/2010
CDRH	Class II Special Controls Guidance Document: Powered Muscle Stimulator with Limited Output for Rehabilitation	4/5/2010
CDRH	Class II Special Controls Guidance Document: Powered Muscle Stimulator for Muscle Conditioning	4/5/2010
CDRH	Class II Special Controls Guidance Document: Powered Muscle Stimulator with Limited Output for Muscle Conditioning	4/5/2010
CDRH	Class II Special Controls Guidance Document: Transcutaneous Electrical Nerve Stimulator for Pain Relief Intended for Over the Counter Use	4/5/2010
CDRH	Recommendations for Premarket Notifications for Lamotrigine and Zonisamide Assays	8/6/2010
CDRH	Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection of Helicobacter pylori	9/23/2010
CDRH	Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection of Clostridium difficile	11/29/2010
CDRH	Establishing the Performance Characteristics of Nucleic Acid-Based In Vitro Diagnostic Devices for the Detection and Differentiation of Methicillin-Resistant Staphylococcus aureus (MRSA) and Staphylococcus aureus (SA)	1/5/2011
CDRH	Recommended Warning for Surgeon's Gloves and Patient Examination Gloves	2/7/2011
CDRH	Processing/Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling	5/2/2011

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CDRH	Establishing the Performance Characteristics of In Vitro Diagnostic Devices for Chlamidia trachomatis and/or Neisseria gonrrhoea: Screening and Diagnostic Testing	5/11/2011
CDRH	Class II Special Controls Guidance Document: In Vitro Diagnostic Devices for Bacillus spp. Detection	5/18/2011
CDRH	Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection of Methicillin-Resistant Staphylococcus aureus (MRSA) for Culture Based Devices	6/15/2011
CDRH	Applying Human Factors and Usability Engineering to Optimize Medical Device Design	6/22/2011
CDRH	Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act	8/16/2011
CDRH	Pediatric Information for X-ray Imaging Device Premarket Notifications	5/10/2012
CDRH	Accreditation and Reaccreditation Process for Firms under Third Party Review Program: Part I	2/15/2013
CDRH	Use of International Standard ISO-10993: Biological Evaluation of Medical Devices Part I – Evaluation and Testing	4/23/2013
CDRH	Implanted Blood Access Devices for Hemodialysis	6/28/2013
CDRH	Medical Device Reporting for Manufacturers	7/9/2013
CDRH	Applicability of Good Laboratory Practice in Premarket Device Submissions: Questions and Answers	8/28/2013
CDRH	Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems	8/30/2013
CDRH	Regulatory Requirements for Hearing Aid Devices and Personal Sound Amplification Products	10/10/2013
CDRH	Medical Device Development Tools	11/14/2013
CFSAN	Use of Antibiotic Resistance Marker Genes in Transgenic Plants	9/4/1998
CFSAN	Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering	1/18/2001
CFSAN	Whole Grain Label Statements	2/17/2006
CFSAN	Control of Listeria monocytogenes in Refrigerated or Frozen Ready-To-Eat Foods	2/7/2008
CFSAN	Compliance Policy Guide: Guidance for FDA Staff Sec. 555.320 Listeria monocytogenes	2/7/2008
CFSAN	Guide to Minimize Microbial Food Safety Hazards of Melons	7/3/2009
CFSAN	Guide to Minimize Microbial Food Safety Hazards of Leafy Greens	7/3/2009
CFSAN	Guide to Minimize Microbial Food Safety Hazards of Tomatoes	7/21/2009
CFSAN	Ingredients Declared as Evaporated Cane Juice	10/7/2009
CFSAN	Questions and Answers Regarding the Reportable Food Registry as Established by the Food and Drug Administration Amendments Act of 2007 (Edition 2)	5/25/2010
CFSAN	Acidified Foods	09/27/2010
CFSAN	Dietary Supplements: New Dietary Ingredient Notifications and Related Issues	7/5/2011
CFSAN	Arsenic in Apple Juice - Action Level	7/13/2013

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CFSAN	Questions and Answers Regarding the Final Rule, Prevention of Salmonella Enteritidis in Shell Eggs During Production, Storage, and Transportation (Layers with Outdoor Access)	7/24/2013
CFSAN	Frequently Asked Questions About Medical Foods; Second Edition	8/13/2013
CFSAN	Acrylamide in Foods	11/15/2013
CTP	The Scope of the Prohibition Against Marketing a Tobacco Product in Combination with Another Article or Product Regulated under the Federal Food, Drug, and Cosmetic Act	10/05/2009
CTP	Preliminary Timetable for the Review of Applications for Modified Risk Tobacco Products under the Federal Food, Drug, and Cosmetic Act	11/27/2009
CTP	Submission of Warning Plans for Cigarettes and Smokeless Tobacco Products	09/09/2011
CTP	Applications for Premarket Review of New Tobacco Products	09/28/2011
CTP	Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under the Federal Food, Drug, and Cosmetic Act	04/03/2012
CTP	Modified Risk Tobacco Product Applications	04/03/2012
CVM	#132, "The Administrative New Animal Drug Application Process"	11/6/2002
CVM	#211, "Residual Solvents Q&A"	12/3/2010
CVM	CPG 690.150, "Labeling and Marketing of Nutritional Products Intended for Use to Diagnose, Cure, Mitigate, Treat, or Prevent Disease in Dogs and Cats"	9/10/2012
CVM	#221, "Recommendations for Preparation and Submission of Animal Food Additive Petitions"	9/11/2013
ORA	Guidance for Industry: Regulatory Procedures Manual - Chapter 9, Subchapter: Guidance Concerning Recommending Customs' Seizure and Destruction of Imported Human and Animal Food That has Not Been Reconditioned; Draft Guidance	11/5/2002
ORA	Submission of Laboratory Packages By Accredited Laboratories	1/2009
OSMP	Guidance for the Public and FDA Staff on Convening Advisory Committee Meetings	8/1/2008
OSMP	Classification of Products as Drugs and Devices and Additional Product Classification Issues	6/1/2011
OSMP	Interpretation of the Term Chemical Action in the Definition of Device Under Section 201(h) of the Federal Food, Drug, and Cosmetic Act	6/1/2011
OSMP	Guidance for Industry and FDA Staff: Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA	1/18/2013
OSMP	Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4	4/1/2013