Contains Nonbinding Recommendations

Guidance for FDA Advisory Committee Members and FDA Staff : Voting Procedures for Advisory Committee Meetings

For questions regarding this document, please contact the Advisory Committee Oversight and Management Staff at 301-827-1220

U.S. Department of Health and Human Services
Food and Drug Administration

August 2008

Contains Nonbinding Recommendations

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GUIDANCE FOR FDA ADVISORY COMMITTEE MEMBERS AND FDA STAFF

Voting Procedures for Advisory Committee Meetings

I. Introduction

This guidance provides guidance on advisory committee voting procedures and is intended for use by FDA advisory committee members and FDA staff involved with advisory committee matters. This document recommends uniform procedures that can be used for the voting process when votes are taken during advisory committee meetings. This document does not recommend when votes should be taken.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

FDA's advisory committees provide independent expert advice to the agency on a range of complex scientific, technical, and policy issues, including questions related to the development and evaluation of products regulated by FDA. Advisory committees are a valuable resource to FDA, and they make an important contribution to the agency's decision-making processes. Although advisory committees provide recommendations to FDA, FDA makes the final decisions.

Advisory committees typically communicate advice or recommendations to the agency in two ways. First, FDA learns from the discussion and exchange that occurs among advisory committee members, and from individual recommendations and suggestions made during the discussion of any advisory committee meeting. Second, advisory committees often vote on a question or series of questions posed to the committee during a committee meeting. As the agency makes its final decision, FDA seriously considers the recommendations made by advisory committees, including the advisory committee deliberations and voting.

This document provides guidance on the procedures used for voting.

There are some advisory committee meetings at which votes are not taken. For example, votes are typically not taken at meetings to discuss the development of a clinical trial design or the development of a guidance document.

At other advisory committee meetings, members cast a formal vote on issues related to the approvability of a product submission. In others, different questions may be posed to a committee for a formal vote. Votes can be an effective means of communicating with FDA because they provide feedback on discrete questions. These questions are generally scientific in nature and can involve a range of subjects, including evaluation of post-market safety data or pre-market assessment of a product's risk/benefit profile. Since all members vote on the same question, the results help FDA gauge a committee's collective view on complex, multi-faceted issues. FDA recognizes that many of the questions voted on by advisory committee members are complex and that the discussion that accompanies the voting is important.. The discussion, together with the votes, helps inform the agency's own deliberations on scientific and regulatory matters.

Accordingly, FDA recommends adopting uniform voting procedures to help maximize the integrity and meaning of voting results. In developing these recommendations, FDA is mindful of the legal requirements of the Federal Advisory Committee Act (FACA), other relevant statutes (e.g., the Federal Food, Drug, and Cosmetic Act), regulations (e.g., 21 CFR Part 14), guidance, policies, and the goals of FDA's advisory committee program.

Transparency and public participation are critical features of the advisory committee process. The use of secret ballots, long a hallmark of the American electoral experience, generally is not appropriate in the advisory committee context because the expert opinion of each member should be clearly understood and identified with that expert. Nevertheless, even with public balloting, the voting process can be managed to help maximize the integrity and utility of the outcome.

There has been much discussion inside and outside FDA regarding sequential versus simultaneous voting. Some have expressed concern that sequential voting, in which members cast public votes in turn, has the potential to compromise the integrity of the result.

For example, scholars and social scientists have studied the risk of "momentum" in sequential voting, exploring whether some sequential voters may be influenced, perhaps even subconsciously, by the votes that precede theirs, especially if those votes are nearly identical or signal a clear trend[1]. This potential risk may be aggravated in the advisory committee setting, where votes are often conducted in full view of a passionate public and participatory audience. In the case of sequential voting, there is also a potential risk that comments made by a committee member or a designated federal officer (DFO) during the vote could inappropriately affect the deliberations of those who have not yet voted. Another potential risk is that comments could alter the meaning (or interpretation) of the question at issue in such a way as to cast doubt on whether all the members voted on the identical question.

III. Policy

Accordingly, to help maximize the integrity, consistency, and utility of advisory committee voting results, FDA recommends that the voting process include the following procedures:

- The Chair and DFO of an advisory committee are encouraged to generate a robust discussion about the matter at issue before any voting takes place. As part of this process, the Chair or DFO should encourage the non-voting members to participate in the discussion and should solicit the views of all members so that any comment, insight, or concern that could influence a voter's conclusions on the matter at issue is heard and considered *before* a vote related to that matter occurs, not afterward. The Chair or DFO should also consider in advance of the vote the need for the advisory committee members to have an opportunity following the vote to further explain any important qualifications related to their votes.

- The question presented for a vote should have minimal qualifiers, not be leading, and should avoid the use of double or triple negatives. When presenting a question for a vote, the Chair, DFO, or other senior agency officials should solicit and answer questions about its meaning before the vote begins. The objective is to reduce any potential confusion and maximize the meaning of the voting results by ensuring that the votes are based on a consistent and collective understanding of the question at issue.

- Voting should be done simultaneously. The objective is to avoid any potential order bias associated with sequential voting and thereby enhance the integrity and meaning of the voting results. The committee Chair or DFO has discretion to decide the precise method of voting on a meeting-by-meeting basis. Examples

[1] See, e.g., Callander, S. (2007): "Bandwagons and Momentum in Sequential Voting," *Review of Economic Studies*, 74, 653-684; Banerjee, A. (1992): "A Simple Model of Herd Behavior," *Quarterly Journal of Economics*, 107, 797-817.

include a simultaneous show of hands, a simultaneous show of "yes" or "no" cards, or a balloting method in which members simultaneously cast written votes. The committee Chair or DFO should determine and announce the precise method at the beginning of the meeting. Further, whatever method of voting is employed, the names of the committee members and their respective votes should be read aloud and otherwise made part of the public record shortly after the vote is taken.

- The question put to the vote should not be the subject of further discussion or clarification while the voting is underway (i.e., whereas a discussion and clarification of the question is encouraged before the vote, there should be no discussion of the meaning of the question while members actually cast their simultaneous votes). Once voting on a particular question has begun, that vote generally should not be terminated until the vote is complete. Following completion of the vote, consistent with the first bullet above, advisory committee members may explain their vote. Additional clarification of the question after a vote and a re-vote on a re-worded question may occur at the discretion of the DFO or committee chair.

- In some instances, the Chair of an advisory committee may believe the committee should vote on a related or relevant question not posed by FDA. If the Chair wants to put another question to a vote on his/her own initiative, the Chair should first check with the DFO or other senior FDA officials present to be sure that the question is appropriate for the meeting, that it is consistent with the topic identified in the meeting notices, and that it will not affect the conflict-of-interest screening that had been completed prior to the meeting. If a determination is made that the question should be posed, the Chair should discuss the matter with the committee members before the voting begins to ensure that the committee members collectively understand the question and feel adequately prepared (either through the background materials or their own expertise) to render a meaningful/informed vote on the new question.

- Briefing materials provided to advisory committee members as background materials before an advisory committee meeting should be thorough and, to the extent possible, include the questions that will be voted upon by the committee. The objective is to maximize the meaning and utility of the voting results by ensuring that the voters have had ample opportunity to study background materials before the day of the meeting.

  For more information about FDA's advisory committee procedures, see http://www.fda.gov/oc/advisory/default.htm.

Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: The Open Public Hearing at FDA Advisory Committee Meetings

FINAL GUIDANCE

Comments and suggestions may be submitted at anytime for agency consideration to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that is published in the *Federal Register*.

For questions regarding this document, contact Michael Ortwerth at 301-796-8220.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner

May 15, 2013

Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: The Open Public Hearing at FDA Advisory Committee Meetings

Additional copies are available from:

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http://www.fda.gov/RegulatoryInformation/Guidances/ucm122045.htm

U.S. Department of Health and Human Services
Food and Drug Administration

May 15, 2013

TABLE OF CONTENTS

Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: The Open Public Hearing at FDA Advisory Committee Meetings[1]

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create nor confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The Food and Drug Administration's (FDA's) advisory committees play an essential role in FDA's activities to protect and promote public health through the regulation of human and animal drugs, biological products, medical devices, foods, and tobacco products. FDA's advisory committees provide independent expert advice and recommendations to the Agency on scientific, technical, and policy matters related to FDA-regulated products. Advisory committees enhance FDA's ability to protect and promote public health by ensuring FDA has access to such advice through the public hearing process as provided in existing laws and regulations. Although advisory committees provide recommendations to FDA, FDA makes the final decisions on any matters considered by an advisory committee. General procedures for FDA advisory committees are described at 21 CFR Part 14.

[1] This guidance applies to all FDA advisory committees including the panels of the Medical Devices Advisory Committee. This guidance has been prepared by the Office of Special Medical Programs in the Office of the Commissioner at the Food and Drug Administration.

FDA encourages participation from all public stakeholders in its decision-making processes. Every advisory committee meeting includes an open public hearing (OPH) session, during which interested persons may present relevant information or views orally or in writing (21 CFR 14.25(a)). FDA's regulation, 21 CFR 14.29, requires that a minimum of 60 minutes per meeting be dedicated to an OPH session for oral presentations, unless public participation does not last that long. For meetings that extend more than 1 day and/or meetings with multiple topics, the OPH session can be divided into multiple parts. If there is an overwhelming interest by the advisory committee in a specific topic, then the committee chair[2] may extend the OPH session. The time and location of the meeting and the OPH session is published in the *Federal Register* (21 CFR 14.20) at least 15 days before a meeting.

This guidance is intended to answer questions about how the public may participate at an OPH session. This includes, but is not limited to, general members of the public; individuals or spokespersons from the regulated industry (except the sponsor whose product is under review); consumer advocacy groups; and professional organizations, societies, or associations.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[2] The chair is a committee member appointed to preside at committee meetings and ensure that all rules of order and conduct are maintained during each session (21 CFR 14.30). He or she is typically an experienced committee member.

II. ORAL PARTICIPATION IN AN FDA ADVISORY COMMITTEE OPEN PUBLIC HEARING

A. Providing a Request to Speak at the OPH

An interested person who wishes to be assured of the opportunity to make an oral presentation at an advisory committee meeting should inform FDA orally or in writing before the meeting (21 CFR 14.29(b)). The interested person should submit the request to the FDA contact person designated in the *Federal Register* (FR) notice announcing the advisory committee meeting by the listed deadline date (21 CFR 14.29(b)). FDA staff makes every effort to accommodate a speaker's request. FDA recommends that the request be submitted by mail, telephone, facsimile, or e-mail. If the number of registrants requesting to speak is greater than can be reasonably accommodated during the scheduled open public hearing session, FDA may conduct a lottery to determine the speakers for the scheduled open public hearing session. FDA staff intends to contact speakers regarding their request to speak at least one week prior to the deadline for written submissions announced in the FR notice.

The interested person should include the following with the request:

- Name of the individual or;
- Name of the group, including the name of the spokesperson making the presentation, a description of the constituency that the group represents, and a brief mission statement of the group; and
- Contact information (mailing address, e-mail address, telephone, and fax numbers).

The interested person shall also include the following in the submission:

- A description of the general nature of the presentation, pursuant to 21 CFR 14.29(b)(1). The submitter may include an outline of the presentation to satisfy this requirement. Whenever possible, all written information to be discussed by the submitter at the meeting should be furnished in advance to FDA, pursuant to 21 CFR14.29(b)(1) (see II.D below).
- Amount of time requested for the presentation, pursuant to 21 CFR 14.29(b)(1). The time that FDA allocates to each person who wishes to make a presentation is dependent upon the number of requests. FDA usually allots 5 to 10 minutes per person. However, if a large number of people have requested to address the committee, FDA may reduce the time allotment for each speaker pursuant to 21 CFR 14.29(b)(2) and/or extend the time of the OPH session. In the interest of obtaining as many points of view as possible, FDA may require speakers with similar statements to consolidate their presentations into a single presentation, pursuant to 21 CFR 14.29(b)(2). Alternatively, individuals and/or groups may choose to make a joint presentation. In the interest of fairness, all speakers are asked to adhere to their allotted time. If the number of registrants requesting to speak is greater than can be reasonably accommodated during the scheduled OPH session, FDA may conduct a lottery to determine the speakers for the OPH session. If necessary, FDA may choose to extend the time for the OPH session to accommodate registrants.

Audio-visual/media equipment is available at advisory committee meetings. FDA asks that an interested person provide a written request for use of the equipment along with an electronic version of the presentation or any overheads at least one week in advance of the meeting. The interested person should consult with the FDA Designated Federal Officer (DFO)[3] on issues related to the compatibility of software/hardware for his or her presentation.

B. Confirmation to Speak at the OPH

1. FDA staff intends to contact speakers by e-mail, facsimile, or telephone to confirm their participation.
2. FDA may decline a request to speak at an OPH if the person wishes to address a matter that is unrelated to the advisory committee's work (21 CFR 14.25(a)).
3. As discussed in II.A above, FDA intends to assign a time allocation to each speaker. In the event of scheduling changes and if time permits, FDA staff intends to contact speakers concerning these changes.
4. If a speaker is delayed or is unable to attend the meeting, FDA recommends that an FDA representative be contacted. If the speaker would still like to make a presentation and time and resources permit, it may be possible to arrange for an alternative time to speak during the meeting, to have the speaker's statement read by a speaker representative, or to have the statement, or a summary of the speaker's statement, made part of the public record via the public docket. If the confirmed speaker would like a representative to speak

[3] The DFO who coordinates the activities of the advisory committee serves as the link between committee members, FDA, industry, and the public.

on his or her behalf, the confirmed speaker should provide a written authorization to the designated FDA staff for the substitution. However, once the public hearing portion of the meeting has ended, further oral comments from the public will only be accepted at the discretion of the FDA advisory committee chair.

C. Confirmed Speaker Check-In the Day of the Meeting

1. Check-in is at the registration table. Speakers should introduce themselves to the DFO or other FDA staff. FDA intends to provide a designated seating area for OPH speakers.
2. Speakers should work with the DFO or other designated FDA staff to facilitate their presentation (e.g., slides). Any handouts should be submitted by the deadline listed in the *Federal Register* Notice for the meeting.

D. Submissions and Presentations

1. FDA distributes to the advisory committee before or at the meeting those copies of handouts received from public speakers prior to the deadline announced in the FR notice, pursuant to 21 CFR 14.29(b)(1).

A copy of the written information provided by the speakers is included in the permanent record of the meeting (see 21 CFR 14.60(b)(3)).

E. Logistics of an Oral Presentation

1. FDA recommends that the Chair make a statement at the beginning of the OPH session encouraging committee members that it is appropriate to ask questions of OPH speakers if doing so might lead to information that is helpful to the committee's deliberations. The Chair should remind the public and members of the importance of the OPH session to the advisory committee process and that all speakers should be treated in a courteous and respectful manner.
2. FDA generally will make available to speakers a podium or lapel microphone.
3. A timer is used to monitor each speaker. A visual signal (e.g., green/yellow/red light system), the Committee Chair, or the DFO should alert the speaker when his or her allotted time has nearly expired. If the allotted time ends before the speaker has concluded his or her presentation, the Chair or DFO should advise the speaker to complete his or her final remarks and conclude the presentation. In the event that the speaker chooses not to conclude the presentation after being asked to do so, the microphone may be turned off to end the presentation.
4. When the speaker's presentation concludes, the Chair may ask the speaker to remain at the podium for questions from the advisory committee.
5. All oral statements are recorded in the transcript of the meeting. Meeting transcripts are posted on the FDA web site approximately three to four weeks after the meeting takes place.

III. FINANCIAL DISCLOSURE

The law requires that FDA's advisory committee members who are special Government employees (SGEs) or regular Government employees (RGEs) disclose to FDA potential financial interests related to the topic of the advisory committee meeting, including relationships that they may have with the sponsor and competitors of the product(s) under discussion, when the committee addresses a particular matter involving specific parties[4] or a particular matter of general applicability[5]. The financial interests that must be reported include stocks, grants, consulting, teaching, speaking and writing engagements, expert testimony, patents, and royalties. In addition, the financial interests of a spouse, minor child, employer, officer, director, trustee, or partner are imputed to the committee member.[6]

Likewise, FDA encourages OPH speakers to disclose financial relationships they may have with the topic of the meeting and parties (e.g., sponsor and competitors of the product(s) under discussion). At the commencement of each OPH session, the Chair of the advisory committee meeting should read one of the statements set forth in III.A and III.B below, addressing the issue of financial disclosure for all open public hearing speakers.

A. Instructive Statement for Particular Matters Involving Specific Parties Meetings

[4] See 5 CFR 2640.102(l)
[5] See 5 CFR 2640.102(m)
[6] If a SGE or RGE has certain financial interests, he or she may not participate in the meeting unless granted a waiver for conflict of interest, see 18 U.S.C. 208(b)(1) and (b)(3). The basis for granting a waiver will include, as appropriate, the public health interest in having the expertise of the member with respect to a particular matter. 21 U.S.C. 379(d)-1. When a member is granted a waiver, the financial interest(s) associated with the waiver are posted on FDA's website and read into the transcript of the meeting. *See*, "Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers," http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/LawsRegulationsGuidance/default.htm.

Welcome to the Open Public Hearing. Please state your name, and your affiliation if relevant to this meeting. The Food and Drug Administration (FDA) believes that the Agency and public benefit from a transparent process that helps ensure that FDA decisions are well-informed by the advice and information FDA receives from its advisory committees. If you have any financial interests relevant to this meeting, FDA encourages you to state the interest as you begin. Such interests may include a company's or group's payment of your travel or other expenses, or grant money that your organization receives from the sponsor or a competitor. If you do not have any such interests, you may wish to state that for the record. If you prefer not to address financial interests, you can still give your comments.

B. Instructive Statement on Particular Matters of General Applicability Meetings

Welcome to the Open Public Hearing. Please state your name, and your affiliation if relevant to this meeting. The Food and Drug Administration (FDA) believes that the Agency and public benefit from a transparent process that helps ensure that FDA decisions are well-informed by the advice and information FDA receives from its advisory committees. If you have any financial interests relevant to this meeting, such as a financial relationship with any company or group that may be affected by the topic of this meeting, FDA encourages you to state the interest as you begin. If you do not have any such interests, you may wish to state

that for the record. If you prefer not to address financial interests, you can still give your comments.

After each presentation, the Chair or a committee member may question the person concerning his or her presentation. However, neither the Chair nor any committee member should further question the person regarding any potential financial relationships.

IV. REFERENCES

A. FDA Advisory Committee Home Page – http://www.fda.gov/AdvisoryCommittees/default.htm

B. FDA Advisory Committee Annual Calendar of Meetings (Most current calendar year link can be found on the FDA Advisory Committee Home Page)

C. CODE OF FEDERAL REGULATIONS (21 CFR PART 14) – http://www.gpo.gov/fdsys/bulkdata/CFR/2013

Contains Nonbinding Recommendations

Release of ORA Laboratory Analytical Results to the Responsible Party: Guidance for Food and Drug Administration Staff

You may submit written comments regarding this guidance at any time. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2019-D-1163.

For questions regarding this guidance or additional copies, contact the Office of Regulatory Affairs (ORA) Office of Strategic Planning and Operational Policy (OSPOP) at ORAPolicyStaffs@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Regulatory Affairs
Center for Devices and Radiological Health
Center for Food Safety and Applied Nutrition
Center for Tobacco Products
Center for Veterinary Medicine

March 2019

Contains Nonbinding Recommendations

Release of ORA Laboratory Analytical Results to the Responsible Party: Guidance for Food and Drug Administration Staff[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This document provides guidance for FDA staff regarding the release of final and, in some circumstances, preliminary Office of Regulatory Affairs (ORA) laboratory analytical results to the responsible party.[2] This policy applies to samples collected during FDA regulatory activities and analyzed in ORA laboratories. It applies to FDA personnel assigned to deliver and discuss ORA laboratory analytical results with the responsible party. The policy does not require the responsible party to file a Freedom of Information Act (FOIA) request for the records.[3]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance describes the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

Sample collection and analysis (which may include finished product and environmental samples) are important tools the FDA uses to assess regulatory compliance of FDA-regulated products and ensure public health protection. In general, the FDA does not release the results of any regulatory testing it conducts until its ORA laboratory analytical results are final and the report is completed, accepted by the responsible FDA official, and any protected information is

[1] This guidance has been prepared by the Office of Strategic Planning and Operational Policy, in the Office of Regulatory Affairs, in cooperation with the Center for Devices and Radiological Health, the Center for Veterinary Medicine, the Center for Tobacco Products, and the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

[2] For purposes of this guidance, the term *responsible party* may include an owner, operator or agent in charge of the site where the regulatory sample is collected, or who may otherwise be responsible for the safety of the product sampled. In some circumstances, more than one responsible party may need to be contacted.

[3] FDA may also share records, including ORA laboratory analytical results, with other entities including state and local governments and other federal agencies in accordance with 21 C.F.R. Part 20, Subpart E.

appropriately redacted.[4] The FDA has processes in place for the release of final ORA laboratory data and analytical results to the responsible party from which the samples are collected.[5,6] However, because certain laboratory tests performed in ORA laboratories may take several weeks to complete, it can be necessary for the Agency to share preliminary results with the responsible party before the final results are confirmed.

This guidance provides a standardized policy on the release of final ORA laboratory analytical results for FDA samples. The FDA will generally release such results when doing so would advance public health goals. This guidance clarifies when and how such results could be released. This document also describes the FDA's policy to orally share, under some circumstances, certain preliminary ORA laboratory analytical results (internally referred to as "Cannot Rule Out" (CRO) results) with the responsible party.[7] A CRO result is a preliminary indication that the sample may yield a final result that could present a public health hazard or threat. A CRO result indicates that the laboratory analytical testing is ongoing, and final results have not yet been determined.

Communicating a CRO result before the FDA confirms the final result is intended to provide the responsible party with information to make informed decisions about potential hazards and products on the market, as well as to consider initiating or preparing to initiate appropriate mitigating strategies to address a potential hazard.

III. Policy

A. Proactive release of CRO ORA laboratory analytical results

1. In general, FDA should not share CRO results until testing is completed.

2. However, FDA may orally release CRO results to the responsible party after clearance in accordance with ORA laboratory procedures if the FDA determines that such release is in the interest of public health. FDA's assessment and consideration of when to release CRO results should include, but not be limited to:

    a. The potential consequences of the injury or illness that could be caused by the regulated product, if it is ultimately confirmed to contain a poisonous or deleterious substance(s) or other hazardous substance, or otherwise deemed to represent a public health threat;
    b. Any background information on the danger associated with the poisonous or deleterious substance(s) or other hazardous substance/situation related to the sample under analysis;

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[4] *See* 21 C.F.R. §§ 20.20(a), 20.105; 21 C.F.R. Part 20, Subpart D.
[5] *See* ORA-LAB,5.10 *Reporting Laboratory Data*, https://www.fda.gov/downloads/ScienceResearch/FieldScience/LaboratoryManual/UCM092171.pdf
[6] For the release of ORA food and food-related environmental laboratory analytical samples, see FMD 147 *Communication of Sample Analysis Results for Food Products and Environmental Samples, https://www.fda.gov/downloads/ICECI/Inspections/FieldManagementDirectives/UCM449001.pdf*
[7] Pursuant to 21 C.F.R.§§ 20.21, 20.105(c), when FDA discloses CRO results to the responsible party, the information is immediately available for public disclosure to any member of the public who requests it.

c. Susceptibility of the consumers that could be affected;
d. The accuracy of the screening method; and
e. Whether release of the CRO results would interfere with an investigation or enforcement proceeding.

3. FDA Centers and Offices that should be consulted before orally communicating CRO results to the responsible party, include but are not limited to:

    a. For-cause inspections:
        i. For CRO results for samples collected as part of a for-cause inspection (e.g., follow-up to a recall, patient death/injury, or consumer complaint), ORA should collaborate with the respective Center to coordinate strategy prior to communicating with the responsible party.

    b. Outbreaks and emergencies:
        i. For CRO results that are associated with a human or animal food or cosmetic outbreak being coordinated by the FDA Coordinated Outbreak Response and Evaluation Network (CORE), ORA should collaborate with CORE, the respective Center, and Centers for Disease Control and Prevention (CDC), to coordinate strategy prior to communicating with the responsible party.[8]
        ii. For CRO results associated with other FDA-regulated products related to a public health emergency, ORA should collaborate with the FDA's Office of Emergency Operations and the respective Center to coordinate strategy prior to communicating with the responsible party.

    c. Concerns about the sterility of products labeled "sterile:"
        i. For CRO results associated with sterile injectable, inhalation, topical or ophthalmic drug products, ORA should collaborate with the respective Center or, if necessary, the Counter-Terrorism and Emergency Coordination Staff to coordinate strategy prior to communicating with the responsible party.
        ii. For CRO results associated with sterile medical devices, ORA should coordinate with the respective Center to coordinate strategy prior to communicating with the responsible party.

    d. Other situations associated with a public health risk:
        i. When deemed appropriate by the ORA program director, and in accordance with a strategy developed in collaboration with the respective Center, CRO results may be communicated to the responsible party.

[8] State partners should also be included in communications with the responsible party, in accordance with ORA's Field Bulletin 61: Inviting State Partners on Calls with Firms to Explain CDC Epidemiological or Laboratory Data During Outbreak Investigations.

4. Any release of CRO results should include the disclaimer statement below. When results are communicated orally to the responsible party, the FDA official releasing the CRO results should read the statement to the responsible party and document doing so.

> *Disclaimer: "Cannot rule out" sample results are preliminary in nature. They are being shared at this time for informational purposes only. Although this information should be considered as one component of a larger evaluation of product safety, the FDA's communication of these preliminary results does not imply that any future action by any government agency or private party is necessary or appropriate. Final Office of Regulatory Affairs (ORA) laboratory analytical results will be provided as soon as practicable after they become available. However, you remain responsible for assuring the quality and safety of all products you have released to the market. The FDA is not responsible for the consequences of any private party's decision to act, or to not act, on the "cannot rule out" results. More information about "cannot rule out" ORA laboratory results is available at [Provide link to this guidance].*

B. Release of final ORA laboratory analytical results

Upon request by the responsible party (either received by FDA orally or in writing), the FDA may, at its discretion or if mandated by law,[9] release final ORA laboratory analytical results for samples that were collected during FDA regulatory activities. The final results may be provided to the responsible party without the need to file a request that is formally designated as a FOIA request. Releasing final ORA laboratory analytical results in this manner allows the responsible party to take appropriate action, and/or resume normal operation based on the results.

1. In situations where a responsible party is voluntarily holding product, or holding product under the conditions set forth in the import entry bond, pending final ORA laboratory analytical results, the FDA may orally notify the responsible party of the final laboratory analytical results. Written notification may follow at FDA's discretion or if required by law. FDA personnel should document the details of the notification discussion, as well as the responsible party's response.

2. In limited cases, FDA may withhold the release of ORA laboratory analytical results, e.g. if the release is reasonably expected to interfere with an investigation or enforcement proceeding.

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[9] *See, e.g.*, section 704(d) of the Federal Food, Drug and Cosmetic Act, which requires that, "[w]henever in the course of any such inspection of a factory or other establishment where food is manufactured, processed, or packed, the officer or employee making the inspection obtains a sample of any such food, and an analysis is made of such sample for the purpose of ascertaining whether such food consists in whole or in part of any filthy, putrid, or decomposed substance, or is otherwise unfit for food, *a copy of the results of such analysis shall be furnished promptly to the owner, operator, or agent in charge*." (emphasis added).

Product Recalls, Including Removals and Corrections

Guidance for Industry

The FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov/. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2003-D-0146.

For questions regarding this guidance or additional copies, contact the Office of Regulatory Affairs (ORA) Office of Strategic Planning and Operational Policy (OSPOP) at ORAPolicyStaffs@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Regulatory Affairs
Center for Devices and Radiologic Health
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Food Safety and Applied Nutrition
Center for Tobacco Products
Center for Veterinary Medicine

MARCH 2020

Product Recalls, Including Removals and Corrections

Guidance for Industry

Table of Contents

Product Recalls, Including Removals and Corrections

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction:

This guidance document is intended to provide guidance and recommendations to FDA-regulated industry regarding what information firms should give to the Food and Drug Administration (FDA) and how they should notify their customers about product recalls. This guidance is intended to assist those members of industry regulated by the FDA in handling most aspects of a product recall, as well as some removals and corrections which do not meet the definition of a recall under 21 CFR 7.3. The guidance includes a checklist of documentation and information that industry can provide to the FDA that will be used by FDA to evaluate, classify, monitor and audit product recalls. Various statutory provisions and regulations, described below, authorize the FDA to require recalls of certain products in particular circumstances. Additionally, subpart C of part 7 of FDA regulations (21 CFR 7.40-59) provides general guidance for the voluntary recall of products, including those recalls initiated by a firm on its own and at the FDA's request. This guidance provides more specific recommendations and applies to voluntary and, to the extent that the guidance does not conflict with statute or regulation, mandatory recalls of all FDA-regulated products (i.e., food, including animal food; drugs, including animal drugs; medical and radiological devices and products; cosmetics; tobacco products; and biological products.)

Certain statutory provisions authorize mandatory recalls of infant formula (FD&C Act § 412(e)-(g) [21 U.S.C. § 350a(e)-(g)]), medical devices (FD&C Act § 518(e) [21 U.S.C. § 360h(e)]),

food (FD&C Act § 423 [21 U.S.C. § 350l]), tobacco products (FD&C Act § 908(c) [21 U.S.C. § 387h(c)]), electronic products (FD&C Act § 535 [21 U.S.C. § 360ll]), controlled substances (FD&C Act § 569D [21 U.S.C. § 360bbb-8d]), and biological products (Public Health Service Act § 351(d) [42 U.S.C. § 262(d)]). Additionally, FDA regulations set forth specific requirements for mandatory infant formula recalls (subpart E of 21 CFR part 107), medical device corrections and removals (21 CFR part 806), mandatory device recalls (21 CFR part 810), electronic product notifications and corrections (21 CFR parts 1003 and 1004) and mandatory recalls for human cells, tissues, and cellular and tissue-based products (subpart F of 21 CFR part 1271). In addition to the requirements in these statutory provisions and regulations, the guidance's specific recommendations may also be useful for these types of recalls. In the context of a mandatory recall, those conditions in the guidance that are set forth in a statute and/or regulation are requirements, rather than recommendations.

The FDA believes that expediting recall activities is vital . Recalling firms are urged to notify the appropriate FDA Division Recall Coordinator (DRC) or Center contact as soon as a decision is made that a recall is appropriate and, if feasible, prior to the issuance of a notice to the public or written communications to customers. To locate your recall coordinator, please check the following website: https://www.fda.gov/safety/industry-guidance-recalls/ora-recall-coordinators.

After the decision to recall is made, we recommend that you establish communication with a DRC or Center contact and submit the information outlined in this guidance to your FDA contact as soon as possible. We also recommend that you submit information as it becomes available to you rather than waiting until all applicable information is ready. This will allow the FDA the opportunity to review and comment on your recall strategy and to offer guidance and assistance in your recall process.

FDA guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidance means that something is suggested or recommended, but not required.

II. Recall Information Submission to the FDA

We recommend that you include the following information in your recall submission to the FDA, as applicable to the type of product being recalled:[1,2]

1. PRODUCT INFORMATION. We recommend you provide the following:
    - Product name (include brand name and generic name)
    - Model, catalogue, or product order number(s)
    - Product image
    - Description of the product
        - Include if the product is powder, liquid, tablet, capsule, etc.
        - Include the intended use or indications.
            - For animal products, include the intended species and life stage
        - If the product is perishable, include the expected shelf life.
        - Include the type of packaging (i.e., box, flexible plastic, glass, bulk).
        - Two complete sets of all labeling. Include:
            - Product labeling (including all private labels)
            - Individual package label
            - Case label (photocopy acceptable)
            - Package inserts
            - Directions for use
            - Promotional material (if applicable)

Additional recommended information for ***Drug*** recalls:

[1] The recommendations in Section II do not apply to products regulated by FDA's Center for Biologics Evaluation and Research (CBER). CBER has established the Direct Recall Classification program as the primary means by which firms communicate with CBER regarding a recall. Further information on the Direct Recall Classification program may be found at https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/BiologicalProductDeviations/ucm172970.htm.

[2] Some information is required to be reported for certain products, such as medical device corrections and removals under 21 CFR 806.10. Firms should be familiar with mandatory reporting requirements specific to their product even if they are not noted in this guidance.

- NDA/ANDA/(C)NADA/ANADA/MIF Number
- NDC Number
- Indicate if the drug is prescription or OTC
- Indicate the strength
- Describe the route of administration
- Blue Bird label (for Type A medicated articles for animals)

Additional recommended information for ***Medical Device*** recalls:

- 510(k)/IDE/PMA number
- Specifiying whether the medical device is for human and/or animal use

Additional recommended information for Electronic Product notifications and corrections, if applicable:

- Provide responses to the requirements of 21 CFR 1003 and 1004
- Performance Standard

2. CODES (Production Identification Numbers). We recommend you provide the following:

    - Lot/Unit Numbers
        - NOTE: If "all lots" are involved or the product is not coded, explain how non-recalled, or reintroduced product may be distinguished from product subject to recall.
        - Provide an explanation of the lot number coding system, including specific codes for impacted products
    - Expiration date(s) or use-by date(s) or expected shelf life of product.
    - Serial numbers (medical devices)
    - UPC codes
    - UDI (if applicable)
    - Product Code (medical devices/electronic products)

3. RECALLING FIRM. We recommend you provide the following:

-
- Firm name, address, city, state, zip code
- The firm type (e.g., manufacturer, importer, broker, repacker, own-label distributor)

Contacts for Recalling Firm:

- Name, title, phone number, fax number, and e-mail address for recall contact (the person corresponding with FDA about the recall)
- Name, title, address, phone number, fax number, and e-mail address of the most responsible individual (e.g., owner, plant manager, agent-in-charge)
- Name, title, phone number, fax number, and e-mail address for public contact

4. MANUFACTURER. We recommend you provide the following:
   - Firm name, address, city, state, zip code
   - FDA registration number, ifapplicable.
5. IDENTIFY THE FIRM RESPONSIBLE FOR THE VIOLATION/PRODUCT PROBLEM. We recommend you provide the following:
   - Firm name, address, city, state, zip code
6. REASON FOR THE RECALL. We recommend you provide the following:
   - The date the firm made the decision to conduct a recall
   - Explain in detail how the product is violative.
   - Explain how the violation affects the performance and safety of the product. (Also see #7, Health Hazard Assessment.)
   - If the recall is due to the presence of a foreign object, describe the foreign object's size, composition, hardness, and sharpness.
   - If the recall is due to the presence of a chemical contaminant (e.g., cleaning fluid, machine oil, paint vapors), explain the level of contaminant in the product. If applicable, provide the labeling, a list of ingredients and the Safety Data Sheet for the contaminant.

- If the recall is due to a failure of the product to meet product specifications, provide the specifications and report all test results. Provide copies of any sample analysis.
- If the recall is due to the presence of a pathogen, provide the test results if requested.
- If the recall is due to a label issue (e.g., a missing or inaccurate ingredient list), provide and identify the correct and incorrect label(s), description(s), and formulation(s).
- Explain how the problem occurred and the date(s) it occurred.
- Explain how the problem was discovered and the date it was discovered.
- Explain if the problem affects all units subject to recall, or just a portion of the units in the lots subject to recall.
- Explain why this problem affects only those products/lots subject to recall.
- Provide detailed information on complaints associated with the product/problem, such as reports of adverse events:
  - Date(s) of complaint(s)
  - Number of complaints
  - Description(s) of complaint(s) – include details of any injury or illness and, if medical attention was sought, any confirmed diagnoses
  - Lot Number(s)/Serial Number(s) involved
  - Medical Device Complaints – include copies of MedWatch-MDRs
- If a state agency is involved in this recall, identify the agency and a contact.
- Drug recalls (NDA/ANDA/(C)NADA/ANADA/Index Listed products) - provide details for any Field Alert submitted

7. HEALTH HAZARD ASSESSMENT. We recommend you provide the following:
   - Your assessment of the health hazard associated with the violation.
     - NOTE: A recall decision does not depend solely on the health risk of the product. Violative products where no health hazard exists are still in violation of the law and may warrant being voluntarily recalled.

8. VOLUME OF RECALLED PRODUCT. We recommend you provide the following:
    - Total quantity for recall
    - Date(s) produced
    - Quantity distributed
    - Date(s) distributed
    - Quantity held by recalling firm and its distribution centers.
    - How the product is being quarantined
    - If the information is readily available, estimate the amount of affected product remaining in the marketplace for the following direct accounts consignees (customers you sell directly to):
        - wholesale level
        - distributor level
        - retail level
        - pharmacy, clinic, or veterinary level (drugs)
        - consumer or user level, where appropriate (e.g., medical devices)
    - The status/disposition of marketed product, if known, (e.g., used, implanted, used in further manufacturing, or destroyed).
9. DISTRIBUTION PATTERN. We recommend you provide the following:
    - Number of direct accounts by type, for example:
        - wholesalers/distributors
        - repackers
        - manufacturers
        - retail
        - pharmacy/clinic/veterinarian
        - users (medical devices – hospitals, clinics, laboratories)
        - consumers (internet or catalog sales)

- federal government
- foreign (specify whether they are wholesale distributors, retailers or users)

- Geographic areas of distribution, including foreign countries.
- A direct account list (name, address, city, state, contact name, phone number) to the DRC. At minimum, the list should include the "ship to" addresses. If available, provide a copy of this list in a sortable electronic spreadsheet format (e.g., a Microsoft Excel file.) When feasible, you should include other relevant fields in the spreadsheet that might help facilitate follow-up by FDA (e.g., lot numbers, shipment dates) You should include any foreign customers and federal government customers (e.g., USDA agencies, Department of Veterans Affairs, Department of Defense).
    - Indicate what the list represents (i.e., all customers who were shipped recalled product; all customers who were *sold* recalled product; all customers who *may have* been shipped or sold recalled product because it was sold to them within the applicable time period). Most FDA-regulated products are subject to regulations that require distribution recordkeeping.[3] To the fullest extent available or required, as applicable, you should provide an exact distribution list (not a "may have" list) for the recalled lot(s).
- Was product sold under a government contract? If yes, provide the contract number, contract date and implementation date. If no, indicate so.
- Was product sold to any federal, state, or local agency involved in a school lunch program? If yes, list the customers and provide the quantity sold, the sale date and the shipment date.

In addition, we recommend that you notify both "ship to" and "bill to" customers of the recall so that:

- "Ship to" customers can retrieve the product from their location.

[3] For various requirements related to distribution recordkeeping see, e.g., 21 CFR 211.196 (human and animal drugs); 21 CFR 820.160 (medical devices); 21 CFR 117.139 (human food) 21 CFR 111.475 (dietary supplements); 21 CFR 106.100(g) (infant formula); 21 CFR 113.100(f) (low acid foods); 21 CFR 114.100(d) (acidified foods); 21 CFR 507.38 (animal food); 21 CFR 226.110 (Type A medicated articles); 21 CFR 225.202 (medicated animal feed); 21 CFR 1270.35(c) (human tissue); 21 CFR 1271.265(e) (human cells, tissues, and cellular and tissue-based products); and 21 CFR 1.980(k) and 800.55(k) (post administrative detention recordkeeping).

- "Bill to" customers, if responsible, can initiate the sub-recall.[4]

10. RECALL STRATEGY. We recommend you provide the following:

    - Indicate the level in the distribution chain to which you are extending the recall. (e.g., wholesale, retail, pharmacy, or consumer/user, such as patient or physician)

        - If your recall only extends to the wholesale/distributor level, then we recommend that you explain your rationale for not recalling to retail/pharmacy/user level.

    - Indicate the scope of the recall (i.e., which lots are affected). Indicate your strategy for expanding the scope of the recall should additional lots be shown to be affected.

    - Indicate the method of recall communication (e.g., mail, phone, facsimile, e-mail). We recommend that you include a written communication so customers will have a record of the recall and your instructions.

    - When your customers of the recalled lot(s) can be quickly determined with accuracy and completeness (e.g., via distribution records), we recommend directing recall communications to *only* those customers who received the recalled lots. Although indiscriminately sending the notification to all customers may be simpler, this practice desensitizes customers to recall notices, many of whom receive hundreds of inapplicable recall notices per year. If used, indicate how written communications will be sent to customers (e.g., e-mail, overnight mail, first class mail, certified mail, facsimile).

    - If initial communication is made by phone, provide a copy of the phone script.

    - If you have a web site, consider posting the recall communication on the web site as an additional method of customer notification about the recall. (Note: This is not recommended as a sole means of customer notification.)

    - Provide what you have instructed customers to do with the recalled product.

    - Identify a recall contact for each customer and address recall communications to those recall contacts to reduce the potential for the communication letter to get misdirected.

[4] Sub-recalls occur when a consignee further distributes a recalled product without changing the product. A sub-recall is an action taken by that consignee to notify its own accounts.

- If the product should be returned, refunded, or replaced, explain the mechanics of such process.
- If this recall will create a market shortage that may impact consumers, explain the situation and provide any draft plan to address the shortage.
- Describe your recall effectiveness check strategy. Include your strategy for how to track and identify your customers who fail to respond to your recall communications, and what additional steps you will take to notify non-responsive customers.
- Determine and provide your course of action for out-of-business customers of the recalled product.
- Provide a proposed method for destroying the recalled product, if applicable.
- If the product can be reconditioned (brought into compliance with the law), explain how and where the reconditioning will take place. Please provide details of the reconditioning plan to your FDA contact before implementation. All reconditioning must be conducted under any applicable current good manufacturing practices.
    - Describe how the recalled (i.e., pre-reconditioned) product will be segregated and identified so it is not confused with reconditioned product. Reconditioned product needs to be similarly distinguished from product subject to recall that has not been reconditioned.

In addition, we recommend that:

- You contact your FDA DRC prior to product destruction. The FDA will review your proposed method of destruction and may choose to witness the destruction.
- You and your customers keep adequate documentation of product destruction (regardless of whether destruction was witnessed by an FDA investigator).
- Field corrections (e.g., product relabeling) be performed by recalling firm representatives, or under their supervision and control. We do not recommend that a disinterested party such as a wholesaler or retailer be responsible for field corrections. For drug recalls: misbranded drugs for re-labeling should be returned to the recalling firm.
- You contact your DRC prior to releasing reconditioned goods.

III. Recall Notice to Direct Account Consignees

1. For guidance on issuing public warnings, please reference FDA's guidance on Public Warning and Notification of Recalls Under 21 CFR Part 7, Subpart C (issued in February, 2019 https://www.fda.gov/downloads/Safety/Recalls/IndustryGuidance/UCM592851.pdf)

2. GUIDANCE FOR WRITTEN RECALL COMMUNICATIONS TO DIRECT ACCOUNT CONSIGNEES: **Recall communications** should be flagged in large bold print "**URGENT: [insert "FOOD," "DRUG," "MEDICAL DEVICE," etc.] RECALL [or CORRECTION].**" If used, envelopes should be similarly flagged. The terms "market withdrawal" or "stock recovery" should not be used because they have separate regulatory definitions and do not accurately convey the definition of a recall.[5] The FDA recommends that you include the following information in a written recall communication to your direct account consignees:

    a. PRODUCT IDENTIFICATION:

        - Include an accurate and complete description of the product and any codes used to identify the product, e.g., lot/unit numbers, expiration date, serial numbers, catalog numbers, model numbers, UDI, and UPC codes.

        - Consider including a copy of the product label with the recall communication. This could be helpful in identifying and removing the recalled product.

    b. DESCRIPTION OF THE PROBLEM:

        - Identify the reason for the recall and any potential health hazard(s) associated with it. Ensure the statement is clear, directly conveys the risk, and prompts an urgent response by the reader.

    c. DEPTH OF THE RECALL:

        - The recall communication should clearly identify the depth to which the recall is to extend (e.g., wholesale, retail, consumer or user level). For example, if the recall is to the retail level, a statement should read "This recall should be carried out to the retail level."

        - If the product could have been further distributed by your direct account consignees to their customers, then you should include instructions to sub-recall. Sub-recall instructions should also include a statement about the depth of the recall, e.g., "If you have further distributed this product,

[5] See 21 CFR 7.3(g), (h), (j), and (k) for the definitions of "recall," "correction," "market withdrawal," and "stock recovery," respectively.

please identify your customers and notify them at once of this product recall. This recall should be carried out to the retail level."

- If your direct account consignees are instructed to conduct sub-recalls, we recommend that you provide them with the date range that the recalled product was distributed. Wholesalers/ distributors may need this information to identify customers they shipped/sold recalled product to.
- If applicable, consider providing a sub-recall letter with your communication package for your direct account consignees to further notify their sub accounts. This better ensures that the information provided to sub accounts is accurate and complete.

d. INSTRUCTIONS:

- Your recall instructions to your direct account consignees should be clear. For example:
  - Remove product from sale
  - Cease distribution
  - Sub-recall (if appropriate)
  - Return or correct product
- Include a return response card/form. Your direct account consignees should be asked to indicate whether they followed every instruction on the return response card/form. Include a space for the consignee's signature and date.

We recommend that you provide examples of all recall communications (including letters, attachments, envelope) to your DRC.

3. IMPORTANT: All customers in the distribution chain should be ***notified*** of the recall, preferably in writing. Here are some examples of why this is important.

   a. In the case of a human drug recall, the FDA does not believe it is appropriate for a sales representative to visit a doctor's office and remove product without notifying the physician or responsible staff of the recall. Physicians may be treating patients that may suffer or have suffered some adverse effect from the drug subject to recall. With knowledge of the recall and the reason for the recall,

the physician can better evaluate a patient's condition and provide appropriate patient care.

b. In the case of products sold at retail stores, the FDA does not believe it is appropriate for a product salesperson or broker representative to remove product from retail shelves without informing store management of the recall. Failure to inform store management of the recall could result in product that is in storage, in transit to the store, or returned by customers, being offered for sale at a later time. The salesperson or broker representative may not have knowledge of or access to the recalled products stored in back rooms. Recalled products that are in-transit to the store could inadvertently be sold to customers. Recalled products returned by customers could inadvertently be placed back on store shelves.

IV. Evaluation of the Recall

1. EFFECTIVENESS OF THE RECALL:

You should ensure that your recall is effective. Therefore, we recommend that you consider effectiveness checks for every recall. The purpose of an effectiveness check is to verify your recall communication was received by your direct account consignee, and that they understood and followed the recall instructions. The effectiveness check should also verify your recall reached the appropriate level in the distribution chain.

Your effectiveness check is a means of evaluating the effectiveness of your recall. If your effectiveness checks indicate that the recall communication was not received and/or its instructions were not followed, then you should take steps to make the recall effective. These steps may involve using alternative means of contacting your customers or sending out a follow up communication that better identifies the product, better explains the problem and/or provides better instructions to the consignees.

Note: In addition to reviewing the effectiveness checks conducted by a recalling firm, the FDA may also contact a percentage of the firm’s customers (a process referred to as audit checks) as a means of assessing whether the recalling firm and its customers are carrying out the recall. If FDA's audit checks determine the recall to be *ineffective*, the recalling firm (or sub recalling firm if such is the case) will then be requested by FDA to take appropriate actions, such as re-issuing recall communications.

2. RECALL STATUS REPORTS:

You will be asked to provide Recall Status Reports to your DRC after initiating a recall (usually on

a monthly basis but more frequently when indicated). Your Recall Status Reports should usually include the following information:

- Dates and method of customer notification
- Number of customers notified
- Number of customers that responded
- Quantity of recalled product returned or otherwise accounted for
- Number of customers that did not respond (FDA may ask for the identity of such customers)
- Estimated time frame for completion of the recall
- Details of your recall effectiveness checks

3. ROOT CAUSE OF THE PROBLEM THAT RESULTED IN THE RECALL:

It is important to attempt to establish the root cause of a problem that results in a product recall so that appropriate corrective actions can be taken. We recommend that you provide the root cause information to your DRC or appropriate Center contact.

4. CORRECTIVE AND PREVENTIVE ACTIONS TO PREVENT FUTURE OCCURRENCES OF THE PROBLEM:

We recommend that you explain to the FDA the corrective and preventive actions planned or underway that will prevent a similar problem from recurring. You should provide this information to your DRC or appropriate Center contact.

5. TERMINATION OF THE RECALL:

We recommend that you evaluate your recall for termination when all possible customer responses have been received and it is reasonable to assume that the product subject to the recall has been removed and proper disposition or correction has been made commensurate with the degree of hazard of the recalled product. A final Recall Status Report and documentation of recalled product disposition should be provided to your DRC, after which the FDA will consider formal termination of the recall action. See 21 CFR 7.55 Termination of a recall.

Note: Upon receipt of termination information, the DRC may prepare a recall termination document for center and/or division management concurrence. When concurrence is obtained, the FDA division office will notify the recalling firm that the FDA considers the recall terminated.

Additional Guidance and/or Requirements:

21 CFR part 7, subparts A and C – Recalls (general guidelines)
FD&C Act § 412 [21 U.S.C. § 350a] – Requirements for Infant Formulas
21 CFR part 107, subpart E –Infant Formula Recalls
FD&C Act § 423 [21 U.S.C. § 350l] – Mandatory Recall Authority (food)
21 CFR part 1271 – Human Cells, Tissues, and Cellular and Tissue-based Products

Public Health Service Act § 351 [42 U.S.C. § 262] – Regulation of Biological Products
FD&C Act § 518 [21 U.S.C. § 360(h)] – Notification and Other Remedies (medical devices)
21 CFR part 806 – Medical Devices; Reports of Corrections and Removals
21 CFR part 810 – Medical Device Recall Authority
FD&C Act § 908 [21 U.S.C. § 387h] – Notification and Other Remedies (tobacco products)

FD&C Act § 535 [21 U.S.C. § 360ll] – Notification of Defects In, and Repair or Replacement of, Electronic Products

FD&C Act § 569D [21 U.S.C. § 360bbb-8d] – Notification, Nondistribution, and Recall of Controlled Substances
21 CFR part 1003 – Notification of Defects or Failure to Comply (electronic products)
21 CFR part 1004 – Repurchase, Repairs, or Replacement of Electronic Products

For additional information on FDA Guidance for Industry, visit FDA's Guidance for Recalls-Information on Recalls of FDA Regulated Products

Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers

FINAL GUIDANCE

Comments and suggestions may be submitted at any time for agency consideration to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that is published in the *Federal Register*.

For questions on the content of this guidance, contact Advisory Committee Oversight and Management Staff, at 301-796-8220.

U.S. Department of Health and Human Services
Food and Drug Administration

March 2014

Guidance for the Public, FDA Advisory Committee Members, and FDA Staff:

Public Availability of Advisory Committee Members' Financial Interest Information and Waivers

Additional copies are available from:
Advisory Committee Oversight and Management Staff
Office of Special Medical Programs, OMPT
Food and Drug Administration
10903 New Hampshire Avenue,
Building 32, rm. 5103
Silver Spring, Maryland 20993

http://www.fda.gov/RegulatoryInformation/Guidances/ucm122045.htm

U.S. Department of Health and Human Services
Food and Drug Administration

March 2014

Table of Contents

Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers[1]

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to help the public, Food and Drug Administration (FDA) advisory committee members, and FDA staff to understand and implement statutory requirements and FDA policy regarding public availability of information about financial interests and waivers[2] granted by FDA to permit individuals to participate in advisory committee meetings subject to the Federal Advisory Committee Act (FACA) (5 U.S.C. App.). This guidance describes the basis and provides a format for public disclosure of certain financial interests by special Government employees (SGEs) and regular Government employees participating in these advisory committee meetings, and provides a format for FDA waivers allowing participation in these meetings.[3] This

[1] This guidance has been prepared by the Advisory Committee Oversight and Management Staff in the Office of the Commissioner at the Food and Drug Administration.
[2] For purposes of this guidance, the term "waiver" refers to determinations and certifications that the Agency is authorized to issue under 18 U.S.C. § 208(b)(1) and (b)(3), respectively.
[3] *See* "Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees," http://www.fda.gov/RegulatoryInformation/Guidances/ucm122045.htm. That document describes FDA's policy for considering whether an individual invited to participate in an FDA advisory committee meeting

guidance also explains how and when these documents will be made publicly available by FDA.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. APPLICABILITY

This guidance applies to SGEs and regular Government employees invited to participate in FDA advisory committees subject to FACA. The types of advisory committee meetings within the scope of this guidance are meetings involving particular matters as defined in regulations issued by the Office of Government Ethics (OGE). *See* 5 CFR § 2640.103(a)(1).[4]

III. BACKGROUND AND PURPOSE

Advisory committees provide independent, expert advice on scientific, technical, and policy matters related to the development and evaluation of products regulated by FDA, such as human and animal drugs, biological products, medical devices, foods, cosmetics, and tobacco products. The advisory committee system enhances FDA's

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has a potential conflict of interest under 18 U.S.C. 208 and whether, under the statute, a waiver to allow participation in an advisory committee meeting is appropriate.

[4] Particular matters involve deliberation, decision, or action that is focused upon the interests of specific persons or a discrete and identifiable class of persons, and include matters involving specific parties and matters of general applicability. *See also* 5 CFR § 2640.102(l)-(m).

ability to protect and promote the public health and maintain the public trust by enabling the agency to obtain the benefit of independent, professional expertise. Although advisory committees provide recommendations to FDA, final decisions are made by FDA. *See* 5 U.S.C. App. 2 § 9(b); 21 CFR § 14.5.

Most FDA advisory committee members are appointed as SGEs. Advisory committee members may also be regular Government employees; for example, FDA may request participation by employees of the United States Department of Agriculture, the Centers for Disease Control and Prevention, or other Federal agencies for matters where such employees' expertise is needed.

FDA implements a rigorous process for soliciting and vetting candidates for advisory committee meetings to minimize any potential for financial conflicts of interest. In preparation for advisory committee meetings involving particular matters, SGEs invited to participate in the meetings are required to report to FDA any financial interests related to the subject matter of the advisory committee meeting. *See* 5 CFR § 2634.904(a)(2). Regular Government employees also report financial interests on a yearly basis and/or just prior to the advisory committee meeting they are planning to attend. *See* 5 CFR §§ 2634.202 and 2634.904(a)(1). FDA reviews these reports, called Confidential Financial Disclosure Reports[5] in advance of each upcoming meeting, once

[5] In rare cases, an individual who is a regular Government employee may file a Public Financial Disclosure Report.

the meeting topics have been identified, to determine whether any financial conflicts of interest may exist for these individuals.[6]

FDA seeks to identify all potential financial conflicts related to the particular matter before a committee. FDA reviews not only the financial interests of a potential advisory committee participant and his immediate family, but also the financial interests, of which he has knowledge, of the participant's business partners, organizations for which he serves as officer, director, trustee, general partner, or employee, and any prospective employer of the member (if there are ongoing employment negotiations or an agreement regarding future employment). *See* 18 U.S.C. § 208(a).

FDA is authorized by statute to grant waivers to allow individuals with potentially conflicting financial interests to participate in meetings where it concludes, after close scrutiny, that certain criteria are met. *See* 18 U.S.C. § 208(b)(1) and (b)(3). The Agency has also issued a guidance document describing our policy for considering eligibility for advisory committee participation.[7]

This document contains revisions to reflect the statutory changes in FDA's authority after the implementation of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), and replaces previous guidance of the same title.[8]

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[6] In addition, FDA screens advisory committee members broadly for covered relationships that could present even the appearance that they have conflicts of interest that could affect their impartiality. *See* 5 CFR § 2635.502. This guidance does not address this screening process.

[7] *See* FDA's "Guidance for The Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees" http://www.fda.gov/RegulatoryInformation/Guidances/ucm122045.htm. All guidance documents relevant to Advisory Committee matters may be accessed at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm122045.htm

[8] Section 712 of the FD&C Act requires that FDA review its disclosure guidance at least every 5 years, and update guidances as appropriate. This revision is a result of that review.

IV. LEGAL FRAMEWORK

Members of FDA's advisory committees are subject to government wide conflict of interest statutes and standards of ethical conduct regulations. A federal conflict of interest statute, 18 U.S.C. § 208, prohibits an SGE or regular Government employee with a financial interest that can be affected by the particular matter before the advisory committee from participating in the advisory committee meeting unless a waiver is granted or the financial interest is covered by one of the regulatory exemptions found at 5 CFR Part 2640. The statute is applicable government-wide, and specifies the circumstances under which FDA may grant waivers to permit participation in specific meetings. An additional statutory requirement applies to FDA advisory committees. FDA is directed to disclose on its website the type, nature, and magnitude of the financial interests of each advisory committee member who has received a waiver under 18 U.S.C. § 208 and the reasons for granting each waiver prior to the advisory committee meeting, including, as appropriate, the public health interest in having the expertise of the member with respect to the particular matter.[9] A waiver for an SGE must be based on a determination that the need for the SGE's service outweighs the potential for a conflict of

[9] This statutory disclosure requirement has changed over time. For example, under § 505(n)(4) of the FD&C Act, enacted as part of the Food and Drug Administration Modernization and Accountability Act of 1997, advisory committee members serving on panels related to new drugs could only receive a waiver of a conflict of interest requirement "upon public disclosure of such conflict of interest if such waiver is necessary to afford the panel essential expertise." The Food and Drug Administration Amendments Act of 2007 repealed § 505(n)(4) and enacted § 712. As enacted at that time, § 712 also contained provisions regarding waivers of conflicts of interests and public disclosures of such waivers. It had several differences from § 505(n)(4), including that it extended its conflict of interest rules to all FDA advisory committee members. In 2012, Congress enacted FDASIA, which amended § 712, including by removing the "essential expertise" agency-specific waiver standard. The requirement to make disclosures of waivers is now in § 712(c).

interest. This information must be published within specified time frames before advisory committee meetings. *See* § 712(c) of the FD&C Act.

In addition to these statutory requirements regarding the disclosure of information about financial interests and corresponding waivers, FDA also has the authority to establish policies regarding the operation of advisory committees and participation of advisory committee members. *See* 21 U.S.C. § 393; 41 CFR §§ 102-3.105 and 102-3.130.

V. DISCLOSURE OF CERTAIN FINANCIAL INTERESTS AND WAIVERS

To increase the transparency, consistency, and clarity of the advisory committee process, consistent with the requirements of § 712(c) of the FD&C Act described above, FDA has concluded that it is desirable to implement agency-wide procedures regarding disclosure of financial interest information that apply to all SGE and regular Government employees invited to participate in FDA advisory committee meetings subject to FACA. In preparation for each advisory committee meeting, to ensure individuals understand what information about their financial interests will be made public, FDA intends to request that individuals within the scope of this guidance acknowledge that FDA intends to publicly disclose the type, nature, and magnitude of any waived financial interests. FDA further intends to make the individuals' participation in advisory committee meetings contingent upon their acknowledgement of FDA's intention to publicly disclose this information.

To facilitate such disclosure, FDA plans to prepare a document listing the financial interests for which a waiver is sought. A template that FDA intends to use when preparing this document, based on information already submitted by the individual,[10] is found in Appendix 1. Using the template format, FDA will list personal and immediate family interests separately from other imputed interests. Other imputed financial interests are those that are attributed to the individual through his employer (i.e., the employer has a relevant financial interest) or through his position as an officer, director, trustee, or general partner. Even though the individual may have no personal involvement in these interests, imputed financial interests that can be affected by the particular matter before the advisory committee are considered conflicts of interest under the applicable law.

First, FDA will identify the type of interest. The template provides several examples, such as stocks/investments and employment. Second, FDA will identify the nature of the interest. The template instructs that the name of the company or institution be identified, along with indicating whether the firm is the sponsor, a competing firm, or other affected entity. Third, FDA will indicate the magnitude of an interest by a dollar range, such as $0 to 5000. The agency will request that the individual in need of a waiver review the document and acknowledge his/her understanding that FDA will publicly disclose the information.

FDA does not intend to publicly disclose financial interest information if the information is exempt from disclosure under the Freedom of Information Act or

[10] *See* section III above.

otherwise protected from disclosure by statute or regulation, except if necessary to describe the type, nature, and magnitude of the financial conflict being waived. For example, FDA would not disclose the name of a company or institution in which the committee member has a financial interest if doing so would reveal that company's confidential commercial information.

In addition, FDA is providing a template of the waivers that the agency grants (Appendix 2). FDA intends to write the waivers in a manner to ensure that information protected from disclosure by statute or regulation does not appear in the waivers. The waivers would therefore not typically require redaction when publicly disclosed as described in the following paragraph. However, if confidential information appears in other documents submitted, completed, or generated in the course of FDA's review of financial interests and waiver requests, this information will continue to be protected from public disclosure in accordance with applicable statutory and regulatory requirements. *See, e.g.*, 21 CFR Part 20.

For waivers that are granted, the disclosure statement will be posted on FDA's website, along with the agency's waiver. FDA will post these documents on the FDA website[11] at least 15 days prior to the relevant advisory committee meeting, except for financial conflicts of interest that do not become known to FDA until shortly before the meeting. For conflicts of interest that FDA becomes aware of less than 30 days prior to the meeting and for which a waiver is issued, FDA will post the documents as soon as practicable and no later than the day of the meeting. These time frames are consistent

[11] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/default.htm

with the requirements of section 712(c) of the FD&C Act. The agency also plans to make the disclosure statements and waiver documents public at corresponding advisory committee meetings.

Additionally, FDA plans to post a roster[12] of all advisory committee members expected to attend a specific meeting at the same time briefing materials for that meeting are posted. *See* FDA's Guidance for Industry: Advisory Committee Meetings – Preparation and Public Availability of Information Given to Advisory Committee Members.[13]

[12] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/default.htm
[13] http://www.fda.gov/RegulatoryInformation/Guidances/ucm122045.htm

Appendix 1

Food and Drug Administration Advisory Committee Member Acknowledgment of Disclosure of Financial Interests

Name of Advisory Committee Member:

Committee:

Meeting Date:

I acknowledge that my participation in the advisory committee meeting described above is contingent upon public disclosure of the following financial interest(s) related to the agenda item: [Describe relevant agenda item],

Type of Interest	Nature	Magnitude
I. Personal/Immediate Family		
[Describe type of interest; e.g.: Stocks/investments; Employment; Work as consultant/advisor; Contracts/grants; Patents/royalties/trademarks Work as an expert witness Teaching/speaking/writing]	[Describe nature of interest; i.e.: name of company or institution and whether it is the sponsor, a competing firm, or other affected entity]	[Describe magnitude of interest; e.g.: $0 – 5,000; $5001 – 10,000; $10,001 – 25,000; $25,001 – 50,000]
II. Other Imputed Interests[14]		
[Describe type of interest; e.g.: Stocks/investments; Employment; Work as consultant/advisor; Contracts/grants; Patents/royalties/trademarks Work as an expert witness Teaching/speaking/writing]	[Describe nature of interest; i.e.: name of company or institution and whether it is the sponsor, a competing firm, or other affected entity]	[Describe magnitude of interest; e.g.: $0 – 50,000; $50,001 – 100,000; $100,001 – 300,000; over $300,000]

[14] Other imputed interests include those that are attributed to the individual through his employer (i.e., the employer has a relevant financial interest) or through his position as an officer, director, trustee, or general partner.

I hereby acknowledge that FDA will make this information publicly available if the agency grants a waiver[15] allowing me to participate in the meeting described above. I understand that without public disclosure of these interests, I will not participate in the advisory committee meeting described above.

_____ _____

Signature Date

[15] Includes determinations under 18 U.S.C. § 208(b)(1) and certifications under 18 U.S.C. § 208(b)(3).

Appendix 2

Waiver to Allow Participation in a Food and Drug Administration Advisory Committee Meeting

Name of Advisory Committee Member:

Committee:

Meeting Date:

Description of the Facts on Which the Waiver is Based:

Type, Nature, and Magnitude of Financial Interest(s):

Description of the Particular Matter to Which the Waiver Applies:

Additional Facts (if any):

Basis for Granting the Waiver:

Certification: [Use one of the first two statements when describing a waiver granted under 18 U.S.C. § 208(b), depending on whether the individual is a regular Government employee or SGE.]

_____ The individual may participate, pursuant to 18 U.S.C. 208(b)(1) – The regular Government employee's financial interest is not so substantial as to be deemed likely to affect the integrity of the services provided by that individual.

_____ The individual may participate, pursuant to 18 U.S.C. 208(b)(3) – The need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved.

Limitations on the Regular Government Employee or Special Government Employee's Ability to Act:

____Non-voting

____Other (specify)

_____ _____

Signature Date

Authorized FDA Official

Guidance for Industry

Advisory Committee Meetings — Preparation and Public Availability of Information Given to Advisory Committee Members

For questions regarding this document, please contact the Advisory Committee Oversight Staff at 301-827-1220.

U.S. Department of Health and Human Services
Food and Drug Administration

August 2008

Guidance for Industry

Advisory Committee Meetings — Preparation and Public Availability of Information Given to Advisory Committee Members

Additional copies are available from:

Office of Policy, Office of the Commissioner
Food and Drug Administration
(HF-11)
5600 Fishers Lane
Rockville, MD 20857
301-827-3360
http://www.fda.gov

U.S. Department of Health and Human Services
Food and Drug Administration

August 2008

Guidance for Industry[1] Advisory Committee Meetings — Preparation and Public Availability of Information Given to Advisory Committee Members

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document provides guidance to industry sponsors, applicants, and petitioners (referred to collectively as *sponsors*) who develop, prepare, or submit briefing materials that will be given to advisory committee members as background information before an open FDA advisory committee meeting.[2] This guidance will help sponsors develop, organize, and submit advisory committee briefing materials for public release and should help minimize the time and resources spent in preparing these materials for public availability. The guidance also describes the process FDA intends to follow when we make briefing materials available to the public. In addition, the Appendices provide recommended timelines for preparing and submitting briefing materials to us.[3]

An important goal of this guidance is to help ensure that briefing materials are made available to the public as provided under section 10(b) of the Federal Advisory Committee Act (FACA) (5 U.S.C. App. 2). The guidance includes recommendations on

[1] This guidance has been prepared by a working group with members from across FDA.

[2] Most FDA advisory committee meetings are open to the public. However, sometimes a portion of a meeting will be closed to the public under 21 C.F.R. § 14.27. This guidance only applies to briefing materials prepared for open advisory committee meetings or for the open portions of such meetings.

[3] This guidance, which applies to all FDA open advisory committee meetings or open portions of such meetings, replaces three previously issued draft guidances: 1) "Guidance for Industry: Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of New Drugs and Convened by the Center for Drug Evaluation and Research, Beginning on January 1, 2000" (dated December 1999); 2) "Guidance for Industry: Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of Biologic Products and Convened by the Center for Biologics Evaluation and Research" (dated February 2001); and 3) "Availability of Information Given to Advisory Committee Members in Connection with CDRH Open Public Panel Meetings; Draft Guidance for Industry and FDA Staff" (dated July 18, 2001).

how to identify information that is exempt from public disclosure under the Freedom of Information Act (FOIA) (5 U.S.C. § 552).

Our guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in our guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Relevant Statutes and Regulations

As stated earlier, under section 10(b) of FACA, any materials made available to an advisory committee also must be made available to the public. The public availability of these materials, however, is subject to FOIA, and FOIA exempts certain types of information from public disclosure. We interpret FACA to require that, with respect to any open advisory committee meeting convened pursuant to FACA, whenever practicable and subject to any applicable FOIA exemptions, those materials that we provide to advisory committee members in connection with that meeting must be made available for public inspection and copying ***before or at the time of*** the advisory committee meeting.

Several FDA regulations (e.g., 21 CFR §§ 20.61, 20.63, 171.1, 314.430, 514.12, 601.51, and 860.5) protect information that is exempt from public disclosure under FOIA. We interpret our regulations to be consistent with FACA and intend to exercise our discretion under our regulations in a manner consistent with FACA and FOIA. This guidance should help ensure that information that is exempt from disclosure under FOIA will not be made publicly available.

B. Advisory Committee Meetings – General Information

III.

We convene advisory committee meetings for a variety of different purposes. Some meetings discuss particular matters such as the approval or testing of products. Topics commonly discussed at this type of advisory committee meeting often involve marketing applications/submissions such as:

- New drug applications and application supplements;
- New animal drug applications and application supplements;
- Biologics license applications and application supplements;
- Premarket approval applications for medical devices and their supplements;
- Premarket notifications for medical devices; and
- Medical device classifications and reclassifications.

We also convene advisory committee meetings to discuss general matters, such as guidance documents, issues pertaining to trial design, post-approval monitoring, citizen's petitions, and policy issues related to FDA-regulated products.

III. MAKING BRIEFING MATERIALS AVAILABLE TO THE PUBLIC

A. Scope of Briefing Materials Subject to this Guidance

This guidance uses the term "briefing materials" to describe the package of information that we provide to advisory committee members before a meeting. The briefing materials usually contain information prepared by us and/or the sponsor (if the meeting involves an application or a particular product). Although interested persons (i.e., individuals or organizations who are not sponsors) may submit information to an advisory committee pursuant to 21 C.F.R. §§ 14.29 or 14.35(d), this guidance does not consider those submissions to be "briefing materials."[4]

B. Timelines for Submitting and Making Briefing Materials Publicly Available

For an open advisory committee meeting for which the briefing materials may contain information that, under certain circumstances, could be considered to be exempt from public disclosure under FOIA, we intend (as set forth in the Appendices) to post a publicly available version of the briefing materials on our Web site no later than ***two full business days***[5] before the day the advisory committee meeting (or the part of the meeting to which the materials pertain) is scheduled to occur.

With respect to meetings for which the briefing materials do not contain information that, under certain circumstances, could be considered exempt from public disclosure under FOIA, we will try to make the briefing materials available on our Web site more than two full business days before the day the advisory committee meeting (or the part of the meeting to which the materials pertain) is scheduled to occur. We anticipate that meetings subject to this timeline will normally address general matters such as guidance documents and policy issues related to FDA-regulated products.

Even when a sponsor states that its briefing materials are fully releasable (as described in section IV.D.), we intend to post the briefing materials in accordance with the timelines in the Appendices if the briefing materials contain the type of information that, under certain circumstances, could be considered to be exempt from public disclosure under FOIA. Please note that, as described in the Appendices, we intend to post both sponsor-

[4] Information submitted by interested persons is considered to be publicly disclosable and must conform to the requirements of 21 CFR § 10.20. Failure to comply with the requirements will result in rejection of the submission for filing or, if it is filed, in exclusion from consideration of any portion that fails to comply (21 CFR § 10.20(c)(6)).

[5] In this guidance, a "business day" is a day that we are officially open for business.

prepared and agency-prepared briefing materials for a particular advisory committee meeting (or part of a meeting) at the same time.

If an advisory committee meeting is scheduled to address more than one topic, separate briefing materials may be prepared for the different topics on the meeting agenda. For meetings that last more than one day, we intend to post the publicly available version of the briefing materials on our Web site no later than two full business days before the topic to which the materials pertain will be discussed. For example, assume that two drugs, A and B, will be discussed on days 1 and 2 respectively. We would make the briefing materials on drug A available no later than two full business days before the scheduled day 1 of the advisory committee meeting and the briefing materials on drug B available no later than two full business days before the scheduled day 2 of the advisory committee meeting. Please note that the timelines for sponsors to submit materials to us are linked to the first day of the meeting and not to the specific day on which a particular topic will be discussed. Thus, in our example, the sponsor for drug B would have the same deadline for submitting materials to us as the sponsor for drug A, even though the discussions for their drugs (and the posting of their briefing materials) would occur on different days.

The Appendices to this guidance provide timelines for preparing and submitting briefing materials to us. Appendix A provides timelines for FDA-prepared briefing materials and sponsor-prepared briefing materials in those instances where the sponsor states that its materials are fully releasable to the public. Appendix B provides timelines for briefing materials in instances where the sponsor asserts that its materials are not fully releasable. Please note that the timelines in the Appendices do not provide for formal predisclosure notification to sponsors pursuant to 21 CFR § 20.61(e) and (f). The predisclosure notification requirements in that regulation apply only where the disclosure is to be made in response to a specific request for our records. The disclosures contemplated here are not made in response to a request for our records, but to comply with FACA. Nevertheless, the timelines in the Appendices are at least as generous as the timeframes for notification under 21 CFR § 20.61.

This guidance does, however, constitute public notice under 21 CFR §14.35(d)(2) that a sponsor should submit information to us within the timelines listed in the Appendices if the sponsor wants the advisory committee to consider that information before the meeting. If we do not receive a sponsor's briefing materials within the applicable timeline in the Appendices, we do not intend to provide the sponsor's briefing materials to the members of the committee, and the committee will not consider the sponsor's materials before the meeting.

C. Postponing the Public Release of Briefing Materials

On occasion, the issue of whether certain information in the briefing materials should be made available to the public may need to be decided in court. If a federal court directs us to not release information in briefing materials, we will not release that information and

may postpone the advisory committee meeting where the information would have been discussed until the matter is resolved.

IV. PREPARING BRIEFING MATERIALS

The contents of the briefing materials provided to advisory committee members for their review in advance of a meeting differ from meeting to meeting, and the type and amount of information included generally will depend on the type of product or issues to be discussed. Additionally, as indicated in the Appendices, the times by which sponsors should submit briefing materials differ depending on whether the materials contain information that the sponsor claims is exempt from disclosure under FOIA.

It is important to minimize the time we will need to spend reviewing briefing materials, consulting with sponsors, and redacting such materials. The more time we need to complete this process, the earlier the sponsors may need to submit materials for an advisory committee meeting. If the preparation of the materials occurs too far in advance of a meeting, the materials may not adequately address the issues that will be the subject of the meeting because those issues will not yet have been fully identified.

A. General Recommendations on Preparing Briefing Materials

For open advisory committee meetings that involve sponsor-prepared briefing materials, approximately 55 business days before the meeting is scheduled to occur, FDA intends to notify a sponsor that an advisory committee will consider an issue that is directly relevant to the sponsor. We will explain the meeting's focus to the sponsor and also may advise the sponsor about the information it may wish to include in its briefing materials. To facilitate the review and eventual posting of sponsor-prepared briefing materials, we strongly recommend that sponsors submit both paper and electronic versions of their materials. Sponsors should consult the appropriate FDA component about compatible electronic formats and consult the Designated Federal Official[6] for a given meeting to determine the appropriate number of paper copies.[7]

We emphasize that a sponsor's submissions should include only information related to the issue being discussed by the committee. Statements or suggestions that could be viewed as misleading or promotional (e.g., statements that go beyond study conclusions or speculate about clinical or commercial implications not supported by the data) are inappropriate for inclusion in the briefing materials. In addition, statements or language that are defamatory, irrelevant, or intemperate are inappropriate for inclusion in briefing materials and should be avoided.

[6] The Designated Federal Official is a federal employee who is responsible for the overall administrative management of an advisory committee.

[7] If an advisory committee meeting involves advisory committees from different agency components (e.g., a joint meeting of a Center for Biologics Evaluation and Research advisory committee and a Center for Drug Evaluation and Research advisory committee), sponsors should consult the relevant Designated Federal Officials of the two committees as to the Designated Federal Official coordinating the briefing material process.

B. Information in Briefing Materials That Typically Will Be Disclosable Under FOIA

We generally will consider the following information in advisory committee briefing materials to be disclosable without redaction, unless the sponsor demonstrates that disclosure of the information is likely to cause substantial competitive harm:

- Summaries of clinical safety and effectiveness data;
- Summaries of non-clinical safety and effectiveness data;
- Summaries of adverse drug reaction data;
- Written discussion or analysis of safety or effectiveness data relevant to the topic of the meeting;
- A general description (such as that which would typically be included in product labeling) of product functions, mechanics, and/or engineering;
- A general description of physical characteristics and performance parameters;
- Clinical or preclinical protocols or summaries of protocols;
- Statistical protocols and analyses;
- Information that is proposed to be included in product labeling, such as indications and usage, dosage and administration, and safety information such as warnings and precautions;
- Literature references;[8]
- Any other information that has been previously publicly disclosed by the sponsor;
- Copies of the sponsor's slides to be presented at the advisory committee meeting, if included in the briefing materials; and
- Guidance documents.

The above list is neither exhaustive nor absolute.

With regard to certain topics discussed at advisory committee meetings (for example, issues relating to the approval of a pending New Drug Application (NDA), Biologics Licensing Application (BLA), Premarket Approval Application (PMA), 510(k), New

[8] FDA does not post copyrighted materials on its Web site. If sponsors do wish to submit copyrighted materials, they should provide a bibliography of the copyrighted materials that can be posted.

Animal Drug Application (NADA), or a supplement to any of these), some of the information listed above might be considered confidential commercial information at earlier stages of the product development process. However, we believe it is appropriate to make this information available under 21 CFR §§ 20.82, 314.430(d)(1), 514.11(d), 601.51(d)(1), 814.9(d)(1), and/or 171.1(h)(2) (whichever is applicable) at the time of an advisory committee meeting if the information is germane to the issues to be discussed at the meeting. These materials are often necessary to a committee's consideration of the safety and effectiveness of a product being discussed and committees and sponsors routinely discuss such matters at open advisory committee meetings. It is widely understood that, when advisory committees consider such products, the information contained in these materials will be the subject of open discussion.

C. Information in Briefing Materials That Will Typically Be Exempt from Disclosure

We generally will consider the following types of information to be exempt from disclosure under FOIA:

- Information about product functions, mechanics, engineering, and schematic drawings not in the proposed labeling and not within the scope of the agenda for the meeting;
- Proprietary physical characteristics and performance parameters not in the proposed labeling and not within the scope of the agenda for the meeting;
- Manufacturing process information;
- Manufacturing quality control information;
- Clinical raw data; [9]
- Non-clinical raw data;
- Supplier names, customer lists, production costs, inventory information, failure rates of products, production quality control information;
- Information for which the release would constitute an unwarranted invasion of personal privacy; and
- Product formulation information not in the labeling.

The above list is neither exhaustive nor absolute.

The advisory committee members will receive complete copies of the briefing materials, including information that is exempt from disclosure under FOIA. However, we will not include information that is exempt from disclosure under FOIA in the publicly available

[9] For the purposes of this guidance, FDA considers "raw data" to be a complete data set of case report forms, case report tabulations, or line listings. Data that summarize individual or multiple subject outcomes or results are considered summaries. Summaries may include examples of specific findings.

version of the briefing materials, and we will notify the committee members in writing that any such exempt information may not be discussed during any open portion of the advisory committee meeting.

D. Fully Releasable Sponsor Briefing Materials

To shorten the process for complying with FACA's disclosure requirements, we strongly encourage sponsors to submit briefing materials that may be released to the public, in accordance with the timelines in Appendix A, in their entirety without redaction (i.e., that do not contain any information that the sponsor asserts is exempt from disclosure under FOIA). Sponsors also benefit from preparing fully releasable briefing materials because such briefing materials eliminate the need for us to redact trade secret and/or confidential commercial information and, as a result, can be submitted to us closer in time to the advisory committee meeting than briefing materials containing information that the sponsor asserts is exempt from disclosure under FOIA. As a result, sponsors may be able to devote more time to preparing their submissions before the advisory committee meeting occurs (see timelines in the Appendices).

If a sponsor chooses to submit fully releasable briefing materials that it agrees can be posted in accordance with the timeline in Appendix A, it should mark the materials as: *"Advisory Committee Briefing Materials: Available for Public Release."*

When we receive briefing materials marked as fully releasable, we will review the materials for completeness. We will assume that sponsors who mark their materials "Available for Public Release" have carefully reviewed the included materials to make sure that they all may be made available to the public without redaction. Sponsors should not expect us to identify trade secret or confidential commercial information in briefing materials marked as "Available for Public Release." We will, however, review sponsor briefing materials for information that, if publicly released, would constitute a clearly unwarranted invasion of personal privacy, and we will redact such information. This review time is reflected in the timeline in Appendix A. Additionally, as stated in section III.B., and as set forth in Appendix A, FDA intends to post both the sponsor-prepared briefing materials and the agency-prepared briefing materials at the same time. As discussed in section IV.F., and as set forth in Appendix A, the various activities relating to our briefing materials will not have been completed at the time the sponsor submits briefing materials that it indicates are fully releasable.

E. Sponsor Briefing Materials that Contain Information Claimed to be Exempt from Disclosure

A sponsor may elect to prepare advisory committee briefing materials that contain information that it believes is exempt from disclosure under FOIA (see section IV.C. for a discussion of what types of information we generally will consider to be exempt from disclosure). If the sponsor chooses to prepare such briefing materials, it should prepare two versions of its briefing materials at the same time. One version should be complete,

and should include the information that the sponsor believes should not be available for public release. The second version should be a publicly releasable version.

We recommend that, when preparing briefing materials that contain information the sponsor believes is exempt from disclosure, the sponsor should segregate the information it believes is exempt from disclosure from the releasable information (e.g., by placing it in a separate portion of the briefing materials) or clearly identify the specific information that it believes is exempt from disclosure.

The complete version of the briefing materials (that is, the one that would not be available for public release because it includes the information the sponsor believes is exempt from disclosure under FOIA) should be clearly marked as: *"Draft: Advisory Committee Briefing Materials: Not for Public Release: Contains Trade Secret and/or Confidential Commercial Information."*

For the version of the briefing materials that would be publicly releasable, the sponsor should prepare and submit a copy of the ***same*** materials as are included in the version that is not for public release, but this version should indicate what information the sponsor believes is exempt from disclosure under FOIA. Sponsors should indicate the information they believe is exempt by providing a redacted copy. We suggest that, when redacting information, sponsors should identify any proposed deletions and indicate exactly how much material should be redacted. Sponsors can indicate the amount of information that has been removed in several ways. For example, a sponsor could include a statement such as "two paragraphs have been deleted," or "five pages have been removed." For each document or portion of a document that the sponsor believes is exempt from disclosure under FOIA, the sponsor should explain, in detail, why it believes that the information is exempt from disclosure under FOIA. We caution that, to the extent that the sponsor intends to discuss specific information during the open portion of the meeting, it will be difficult for the sponsor to claim that the information is exempt from disclosure under FOIA.

Sponsors should label the redacted copy prominently as: *"Draft: Advisory Committee Briefing Materials: Available for Public Release."*

After we receive the two versions of the briefing materials (the non-public and publicly releasable versions), we will review the briefing materials for completeness and determine if the sponsor appropriately identified exempt information. If we disagree that any of the information the sponsor has redacted is exempt from disclosure under FOIA, we will discuss the matter with the sponsor. When the discussions are concluded, we will notify the sponsor of our final decision. Once we have notified the sponsor of our final decision, no new documents or information may be added to the briefing materials. See the Appendices for details on the timing of this process.

When the sponsor receives our final decision regarding what information, if any, we have determined to be exempt from disclosure under FOIA, the sponsor has four options:

- Option 1: The sponsor may remove from the briefing materials information that we have determined is not exempt from disclosure under FOIA and thus would not be redacted from the materials. The sponsor may reformat the materials accordingly.

- Option 2: If the sponsor accepts our determination as to the releasability of the information in the briefing materials, and there is still information in the materials that we and the sponsor agree is exempt from disclosure, the sponsor should submit a final copy of both versions of the briefing materials. The final documents should be prominently labeled: *"Final: Advisory Committee Briefing Materials: Not for Public Release: Contains Trade Secret and/or Confidential Commercial Information"* and *"Final: Advisory Committee Briefing Materials: Available for Public Release."*

- Option 3: If we and the sponsor agree that no information in the materials is exempt from disclosure under FOIA, then the sponsor should submit a copy marked *"Final: Advisory Committee Briefing Materials: Available for Public Release."*

- Option 4: If the sponsor disagrees with our determination regarding the releasability of information in the briefing materials, the sponsor may seek judicial review in federal court to prevent us from releasing the information. If the sponsor chooses this option, we will not release the information that is in dispute and may postpone the advisory committee meeting where the information would be discussed until the matter is resolved.

When this process is complete, we will send the final version of the sponsor-prepared briefing materials to the advisory committee members in preparation for the scheduled meeting. We will identify for the advisory committee members any information in the materials that is exempt from disclosure under FOIA, and we will advise them that such exempt information may not be discussed during any open portion of the advisory committee meeting. Additionally, if during this process the sponsor has asserted, and FDA has agreed, that certain information in the briefing materials is exempt from disclosure under FOIA, the sponsor should not in turn discuss that information at an open portion of the advisory committee meeting; such public discussion would be inconsistent with the sponsor's assertions regarding the nonpublic status of the information**.**

F. FDA-Prepared Advisory Committee Briefing Materials

For most advisory committee meetings, we prepare our own briefing materials and send them to the advisory committee members. When we have prepared our briefing materials, we will review them to determine if they contain information that, under certain circumstances, could be considered to be exempt from disclosure under FOIA (specifically, confidential commercial or trade secret information belonging to a sponsor). If the materials do not contain information that, under certain circumstances, could be considered to be confidential commercial or trade secret information belonging to a

sponsor, the portions of the timelines (see Appendices) that pertain to sharing our briefing materials with sponsors will not apply. As discussed in section III.B., under such circumstances we will try to post such briefing materials on our Web site more than two full business days before the day the advisory committee meeting (or the portion of it to which the briefing materials pertain) is scheduled to occur.

If we determine that our briefing materials contain information that, under certain circumstances, could be considered to be confidential commercial or trade secret information belonging to a sponsor, the portions of timelines in the Appendices pertaining to sharing our briefing materials with sponsors will apply, and we will send our briefing materials to the sponsor as described in the timelines. If the briefing materials include information pertaining to more than one sponsor, we will send only the relevant portion to each sponsor. We will discuss with each sponsor any disagreements it may have about the disclosability of information in the materials. We note that, in circumstances where the sponsor has submitted briefing materials that it has asserted are not fully releasable, we may already have had discussions with the sponsor regarding the releasability of certain information in the sponsor's briefing materials and have informed the sponsor of our final decision regarding the redaction of information from its briefing materials. Thus, our discussion with the sponsor regarding our briefing materials should focus on new issues and information, and not on issues or information that were previously discussed with the sponsor in the context of the sponsor's briefing materials.

When the discussions of our briefing materials are concluded, we will notify each sponsor of our final decision regarding the public availability of the information in our briefing materials. If the sponsor disagrees with our determination regarding the releasability of information in our briefing materials, the sponsor may seek judicial review in federal court to prevent us from releasing the information. If the sponsor chooses this option, we will not release the information that is in dispute and may postpone the advisory committee meeting where the information would be discussed until the matter is resolved.

G. Posting Briefing Materials on FDA's Web Site

We will post the briefing materials for an open advisory committee meeting subject to this guidance on our Web site at http://www.fda.gov/ohrms/dockets/ac/acwhatsnew.htm. The materials also will be available in hard copy at our Division of Dockets Management's Public Reading Room.[10] We will post only the publicly available sponsor-prepared briefing materials and the publicly available FDA-prepared briefing materials on our Web site.

To avoid any misunderstanding that we have endorsed the contents of a sponsor's briefing materials by posting them on our Web site, we will display the following statement with the sponsor's briefing materials placed on our Web site:

[10] The Public Reading Room is open Monday through Friday, 9:00 a.m. to 4:00 p.m. The Public Reading Room is located at 5630 Fishers Lane, Room 1061, Rockville, Maryland 20857.

> *"The statements contained in this document are those of the product's sponsor. FDA does not necessarily agree with the sponsor's statements. FDA has not made a final determination about the issues described in this document."*

We also may take appropriate action to address any information that may be promotional or misleading, including posting a correction on our Web site.

Please note that if unforeseen difficulties prevent us from posting the briefing materials on our Web site before an advisory committee meeting, we will make hard copies available to the public at the time of the advisory committee meeting.

If you have questions, please refer to the contact information listed below.

- **For briefing materials pertaining to the Center for Biologics Evaluation and Research:**

  Office of Communication, Training, and Manufacturers Assistance, HFM-40
  Center for Biologics Evaluation and Research
  1401 Rockville Pike, Suite 200N
  Rockville, MD 20852
  Phone: 301-827-1800

- **For briefing materials pertaining to the Center for Devices and Radiological Health:**

  Freedom of Information Officer, Joy Lazaroff
  Office of Management Operations
  Division of Ethics and Management Operations, HFZ-23
  Center for Devices and Radiological Health
  7520 Standish Place
  Rockville, MD 20855
  Phone: 301-827-7258

- **For briefing materials pertaining to the Center for Drug Evaluation and Research:**

  Advisors and Consultants Staff, HFD-21
  Center for Drug Evaluation and Research
  5630 Fishers Lane, Room 1093
  Rockville, MD 20850
  Phone: (301) 827-7001

- **For briefing materials pertaining to the Center for Food Safety and Applied Nutrition:**

Freedom of Information Officer, Patricia Gee
Executive Operations Staff, HFS-22
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, MD 20740-3835
Phone: 301-436-2121

- **For briefing materials pertaining to the Center for Veterinary Medicine:**

  Freedom of Information Officer, Marilyn Broderick
  Communications Staff, HFV-12
  Center for Veterinary Medicine
  7519 Standish Place
  Rockville, MD 20855
  Phone: 240-276-9107

- **For briefing materials pertaining to the National Center for Toxicological Research:**

  Rose Huber
  Office of the Director, HFT-1
  National Center for Toxicological Research
  3900 NCTR Road
  Jefferson, AR 72079
  Phone: 870-543-7130

- **For briefing materials pertaining to the Office of the Commissioner:**

  Carlos Peña, PhD, MS
  Office of Science and Health Coordination
  Office of the Commissioner
  5600 Fishers Lane, HF-33
  Rockville, MD 20857
  Phone : 301-827-3340

Appendices

APPENDIX A: TIMELINE FOR OPEN FDA ADVISORY COMMITTEE MEETINGS INVOLVING FDA BRIEFING MATERIALS AND SPONSOR BRIEFING MATERIALS THAT THE SPONSOR STATES ARE FULLY RELEASABLE

FDA Action	Business Days Before Meeting	Sponsor Action
We intend to notify the sponsor that we are taking an issue directly relevant to the sponsor to an advisory committee.	**55**	
	54 through 23	If the sponsor plans to submit briefing materials to FDA that include any information that it believes is exempt from disclosure, the sponsor should follow the timeline in Appendix B, which calls for the submission of those materials on Day 42. Otherwise, the sponsor should prepare its fully releasable briefing materials for submission to agency staff on day 22.
	22	The sponsor should submit its briefing materials to the appropriate agency staff.
We will conduct the following activities: • We will review the sponsor-prepared briefing materials for completeness. • We will review both the sponsor and final agency briefing materials for disclosure. o We will send the complete (unredacted) agency and sponsor briefing materials to the advisory committee members. o We will send a copy of our briefing materials (or relevant portions thereof), as prepared for public release, to the sponsor to review.	**21 through 14**	
We will discuss with the sponsor any concerns it has raised regarding the disclosability of any information in our briefing materials.	**13 through 9**	The sponsor should review our briefing materials (or relevant portions thereof), as prepared for public release. The sponsor may raise with appropriate center staff any concerns it has regarding the disclosability of any information in our briefing materials. The sponsor should inform us whether it

FDA Action	Business Days Before Meeting	Sponsor Action
		disagrees with us regarding the disclosability of any information in our briefing materials.
If the sponsor has raised concerns with us about the disclosability of information in our briefing materials, we will inform the sponsor of our final decision regarding the redaction, if any, of our briefing materials. We will submit both the sponsor's and the agency's briefing materials (as prepared for public release) to our Division of Dockets Management for posting on our Web site.	**7**	
We will post on our Web site both the sponsor's and the agency's publicly available briefing materials.	**No later than 2 full business days before the day on which the sponsor's topic will be discussed**	

APPENDIX B: TIMELINE FOR OPEN FDA ADVISORY COMMITTEE MEETINGS INVOLVING FDA BRIEFING MATERIALS AND SPONSOR BRIEFING MATERIALS THAT THE SPONSOR ASSERTS ARE NOT FULLY RELEASABLE

FDA Action	Business Days Before Meeting	Sponsor Action
We intend to notify the sponsor that we are taking an issue directly relevant to the sponsor to an advisory committee.	**55**	
	42	The sponsor should submit two versions of its briefing materials: a complete (unredacted) version and a redacted version.
We will send copies of both the complete (unredacted) and the redacted sponsor's submissions to the appropriate disclosure staff and a copy of the complete sponsor submission to the appropriate review staff.	**41**	
We will inform the sponsor whether we agree with the sponsor's proposed redactions to the sponsor's briefing materials.	**34**	
If we disagree with any of the sponsor's proposed redactions, we will discuss the redaction of the sponsor's briefing materials with the sponsor.	**33 through 29**	The sponsor may respond to any disagreements we have raised with regard to the sponsor's proposed redactions to the sponsor's briefing materials.
We will inform the sponsor of our final decision regarding the redaction of information from the sponsor's briefing materials.	**28**	The sponsor should decide whether to remove any materials that we have determined will not be redacted and to reformat the materials accordingly. No new documents or information may be added to the briefing materials at this time.
	22	The sponsor should submit the final version or versions of its briefing materials to the appropriate agency staff.
We will conduct the following activities: • We will send the complete (unredacted) agency and sponsor briefing materials to the advisory committee members. • We will send a copy of our briefing materials (or relevant portions thereof), as prepared for public release, to the sponsor to review.	**21 through 14**	
We will discuss with the sponsor any concerns the sponsor has raised regarding the	**13 through 9**	The sponsor should review our briefing materials (or relevant portions thereof), as

FDA Action	Business Days Before Meeting	Sponsor Action
disclosability of any information in our briefing materials.		prepared for public release. The sponsor will discuss with appropriate center staff any concerns it has regarding the disclosability of any information in our briefing materials. The sponsor should inform us whether it disagrees with us regarding the disclosability of any information in our briefing materials.
If the sponsor has raised concerns with us about the disclosability of information in our briefing materials, we will inform the sponsor of our final decision regarding the redaction, if any, of our briefing materials. We will submit both the sponsor's and the agency's briefing materials (as prepared for public release) to our Division of Dockets Management for posting on our Web site.	**7**	
We will post on our Web site both the sponsor's and the agency's publicly available briefing materials.	**No later than 2 full business days before the day on which the sponsor's topic will be discussed**	

Lead in Cosmetic Lip Products and Externally Applied Cosmetics: Recommended Maximum Level Guidance for Industry

Draft Guidance

This guidance is being distributed for comment purposes only.

Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-1130.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

December 2016

Table of Contents

Contains Nonbinding Recommendations

Draft-Not for Implementation

Lead in Cosmetic Lip Products and Externally Applied Cosmetics: Recommended Maximum Level[1] Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration's (FDA or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This guidance provides a recommended maximum level of 10 parts per million (ppm) for lead as an impurity in cosmetic lip products and externally applied cosmetics that are marketed in the United States. FDA (or "we") has concluded that a recommended maximum level of 10 ppm for lead as an impurity in cosmetic lip products and externally applied cosmetics would not pose a health risk. We consider the recommended maximum lead level to be achievable with the use of good manufacturing practices and to be consistent with the 10 ppm maximum lead level for similar products recommended by other countries. For additional discussion of the scientific and legal background and rationale underlying this recommended level, see "Supporting Document for Recommended Maximum Lead Level in Cosmetic Lip Products and Externally Applied Cosmetics" (http://www.fda.gov/Cosmetics/GuidanceRegulation/GuidanceDocuments/ucm517327.htm).

The issuance of this guidance supports our effort to limit human exposure to lead in finished FDA-regulated cosmetic products by educating new manufacturers who wish to enter the market and encouraging current manufacturers to continue to follow or improve on voluntary good manufacturing practices that limit trace amounts of lead as an impurity. This guidance applies to cosmetic lip products (such as lipsticks, lip glosses, and lip liners) and externally applied cosmetics (such as eye shadows, blushes, shampoos, and body lotions) marketed in the United States.[2] This guidance does not apply to topically applied products that are classified as drugs or to hair dyes that contain lead acetate as an ingredient.

[1] This guidance has been prepared by the Office of Cosmetics and Colors in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

[2] Cosmetic lip products are applied to the mucous membrane and therefore are not considered externally applied cosmetics (See 21 CFR 70.3(v)).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. Background

We regulate cosmetics under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and Fair Packaging and Labeling Act (FPLA). These laws require that cosmetics marketed in the United States be safe under their intended and customary conditions of use, and be properly labeled. Cosmetics are not subject to pre-market approval by FDA. However, pre-market approval is required for the color additives used as ingredients in cosmetics.

Although we have not set limits for lead as an impurity in cosmetics, most listed color additives have specifications for lead as an impurity as part of our requirements for their safe use. This guidance supports our effort to limit human exposure to lead in finished products by recommending a maximum level of 10 ppm lead as an impurity in cosmetic lip products and externally applied cosmetics.

The International Cooperation on Cosmetics Regulation and regions such as Canada and the European Union have set a limit of 10 ppm for lead as an impurity in cosmetics based on considerations of a reasonably achievable level, scientific risk assessment, good manufacturing practices, technical feasibility, and appropriate analytical methods (Refs. 1, 2). This guidance is consistent with those efforts.

III. Discussion

A. Recommended Maximum Lead Level in Cosmetic Lip Products and Externally Applied Cosmetics

Between 2007 and 2009, FDA scientists developed and validated a total dissolution method for analyzing lead in lipstick and used this method to determine the lead content in a selection of 20 commercially available lipsticks on the U.S. market (Ref. 3). In 2010, using the same analytical method, we obtained results for lead content in 400 lipsticks and other cosmetic lip products available in the U.S., and in 2012, obtained similar results for an additional 30 cosmetic lip products (Refs. 4, 5, 6, 7). Finally, between 2012 and 2013, we used a more common extraction method for determining lead in an additional 29 cosmetic lip products (Ref. 7). The lead levels found in our surveys ranged from 0.026 ppm (the detection limit of the total dissolution method for the studies) to a maximum of 7.19 ppm in one lipstick. The average lead concentration was 1.09 ppm.

Between 2011 and 2012, we used a total dissolution method to obtain results for lead content in 120 externally applied cosmetic products available on the U.S. market, which included eye shadows, blushes, body lotions, mascaras, foundations, body powders, compact powders,

shaving creams, and face paints (Refs. 6, 7). Between 2012 and 2013, we used the extraction method for determining lead in an additional 86 externally applied cosmetics (Ref. 7). The lead levels found in our surveys ranged from 0.0084 ppm (the detection limit of the total dissolution method for these studies) to a maximum of 14 ppm in one eye shadow and one blush. The average lead concentration ranged from below the detection limit in shaving creams to 4.6 ppm in compact powders.

These surveys indicate that levels of lead in the cosmetic lip products and externally applied cosmetics we have sampled are for the most part well below 10 ppm, leading us to expect that this recommended maximum level is achievable by all manufacturers of these products. However, in our surveys, which do not necessarily reflect the full range of products that are currently on the market, a small number of samples had lead levels that exceed the maximum level we are recommending. Our goal is to ensure that cosmetic lip products and externally applied cosmetics do not contain lead as an impurity at levels that would pose a health risk. We have determined that a maximum level of 10 ppm in cosmetic lip products and externally applied cosmetics would not pose a health risk, but we encourage manufacturers of these products to follow or continue to follow manufacturing practices that allow them to achieve levels of lead lower than 10 ppm whenever feasible.

We have concluded that a maximum level of 10 ppm for lead as an impurity in cosmetic lip products and externally applied cosmetics should be readily achievable by manufacturers that source their ingredients appropriately and use good manufacturing practices. Modern analytical capability permits determination of lead at ppm levels, thus enabling manufacturers to avoid the purchase of ingredients with unacceptably high levels of lead and to determine whether lead is introduced into their products during the manufacturing process.

B. Exposure Assessment and Public Health Impact of Recommended Maximum Lead Level in Cosmetic Lip Products and Externally Applied Cosmetics

As explained in more detail in our supporting document, the routes of exposure to lead from cosmetic lip products are incidental ingestion and dermal absorption and the route of exposure to lead from externally applied cosmetics is dermal absorption. To assess the exposure to lead from cosmetic lip products and externally applied cosmetic products, we assumed these products contain 10 ppm lead because, as noted above, that impurity level should be readily achievable by manufacturers. Additionally, 10 ppm lead is consistent with the 10 ppm maximum lead level for similar products recommended by the International Cooperation on Cosmetics Regulation and regions such as Canada and the European Union.

1. Exposure to Lead from Cosmetic Lip Products

The composition of cosmetic lip products limits the ability for lead present as an impurity to diffuse from a product and be absorbed by the skin. Therefore, dermal absorption of lead from cosmetic lip products is negligible, and we have concluded that systemic exposure to lead from these products is primarily by incidental ingestion.

We used an approach previously employed by FDA for estimating exposure to lead from food to estimate exposure to lead from cosmetic lip products (Ref. 8). We estimated that maximum exposure to 10 ppm lead from a cosmetic lip product is 0.24 µg/day for adults and adolescents age 13 years or older and 0.024 µg/day for children age 12 years or younger (assuming that children age 12 years or younger use 10% as much of these products as adults) (Ref. 9). We determined that the potential elevation of blood lead levels from 10 ppm lead in these products is too small to be measured in routine blood analysis and requires state of the art analytical technology (Ref. 10).

2. Exposure to Lead from Externally Applied Cosmetics

Dermal absorption of lead from externally applied cosmetics is very small. Results for lead uptake by the skin were reported for four lead compounds that resemble cosmetic ingredients (Ref. 11). Based on those data, we estimated that only a very small amount (0.41%) of the lead present as an impurity in an externally applied cosmetic is absorbed by the skin.

The amount of exposure to lead as an impurity in externally applied cosmetics depends on whether the product is a "leave-on" product (such as eye shadow or body lotion) or a "rinse-off" product (such as shampoo or shaving cream). The amount of exposure also depends on how much product is applied to the skin. For example, eye shadows are applied in very small amounts (40 mg/day) and only around the eyes (Ref. 12). Because dermal absorption of lead is so small, we estimated that exposure to 10 ppm lead from an eye shadow is only 1.64×10^{-3} µg/day for adults and adolescents age 13 years or older and 1.64×10^{-4} µg/day for children age 12 years or younger (assuming that children age 12 years or younger use 10% as much eye shadow as adults). This means that exposure to lead from an eye shadow is approximately 150 times lower than exposure to lead from a cosmetic lip product.

The amount of exposure to lead as an impurity in a product such as body lotion is higher because average applications are higher (8.7 g/day) (Ref. 9). Based on body surface area calculations from reported height and weight data, we estimated that children age 6-18 use 65% as much body lotion as adults age ≥19 and children age 1-5 use 34% as much body lotion as adults age ≥19 (Refs. 10, 13). We then estimated that exposure to 10 ppm lead from a body lotion is 0.36 µg/day for adults age ≥19, 0.23 µg/day for children age 6-18, and 0.12 µg/day for children age 1-5. In addition, our surveys found that body lotions actually contain very little lead (0.04 to 0.10 µg/g) (Refs. 6, 7). Therefore, we estimated that exposure to lead from a body lotion containing 0.10 µg/g (0.10 ppm) lead is 0.0036 µg/day for adults age ≥19, 0.0023 µg/day for children age 6-18, and 0.0012 µg/day for children age 1-5, or 67 times lower for adults and up to 20 times lower for children than exposure to lead from a cosmetic lip product.

Exposure to lead from externally applied cosmetics is up to 150 times lower than exposure to lead from cosmetic lip products. Therefore, the potential elevation of blood lead levels from 10 ppm lead in these products is too small to be measured in routine blood analysis and requires state of the art analytical technology (Ref. 10).

3. Public Health Impact of Recommended Maximum Lead Level in Cosmetic Lip Products and Externally Applied Cosmetics

Based on our exposure assessment, we have concluded that a recommended maximum level of 10 ppm for lead as an impurity in cosmetic lip products and externally applied cosmetics would not pose a health risk. The issuance of this guidance supports our effort to limit human exposure to lead in finished FDA-regulated cosmetic products by educating new manufacturers who wish to enter the market and encouraging current manufacturers to continue to follow or improve on voluntary good manufacturing practices that limit trace amounts of lead as an impurity. We consider the recommended maximum lead level to be achievable with the use of good manufacturing practices and to be consistent with the 10 ppm maximum lead level for similar products recommended by other countries.

Lead is a chemical element for which toxicity in humans has been well documented (Ref. 14). It may occur as an impurity in any of the ingredients used in cosmetic lip products and externally applied cosmetics due to its background presence in the environment. Cosmetics manufacturers are responsible for avoiding potentially harmful levels of lead in their finished products. Our data show that over 99% of the cosmetic lip products and externally applied cosmetics on the U.S. market contain lead at levels below our recommended maximum level. Therefore, we encourage firms to continue the manufacturing practices that achieve these lower levels of lead in their finished products.

C. Enforcement Policy for Lead in Cosmetic Lip Products and Externally Applied Cosmetics

FDA is prepared to take enforcement action against any cosmetic lip product or externally applied cosmetic containing lead at levels that may harm consumers. FDA intends to consider several factors in bringing enforcement actions regarding lead in cosmetic lip products and externally applied cosmetics, including the level of lead present, the particular product, and the conditions of use for the product.

IV. References

We have placed the following references on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You may see them at that location between 9 a.m. and 4 p.m., Monday through Friday. As of December 20, 2016, FDA had verified the Web site address for the references it makes available as hyperlinks from the Internet copy of this guidance, but FDA is not responsible for any subsequent changes to Non-FDA Web site references after December 20, 2016.

1. International Cooperation on Cosmetics Regulation, "Considerations on Acceptable Lead Levels in Cosmetic Products," December 2013, available at http://iccrnet.org/topics/.

2. Health Canada, "Guidance on Heavy Metal Impurities in Cosmetics," July 20, 2012, available at http://www.hc-sc.gc.ca/cps-spc/pubs/indust/heavy_metals-metaux_lourds/index-eng.php.

3. Hepp, N. M., Mindak, W. R., and Cheng, J., "Determination of total lead in lipstick: Development and validation of a microwave-assisted digestion, inductively coupled plasma-mass

spectrometric method," Journal of Cosmetic Science, vol. 60, pp. 405-414, 2009.

4. Hepp, N. M., "Determination of total lead in 400 lipsticks on the U.S. market using a validated microwave-assisted digestion, inductively coupled plasma-mass spectrometric method," Journal of Cosmetic Science, vol. 63, pp. 159-176, 2012.

5. U.S. Food and Drug Administration, "Limiting Lead in Lipstick and Other Cosmetics," December 2016, available at http://www.fda.gov/Cosmetics/ProductsIngredients/Products/ucm137224.htm.

6. Hepp, N. M., Mindak, W. R., Gasper, J. W., Thompson, C. B., and Barrows, J. N., "Survey of cosmetics for arsenic, cadmium, chromium, cobalt, lead, mercury, and nickel content," Journal of Cosmetic Science, vol. 65, pp. 125-145, 2014.

7. U.S. Food and Drug Administration, "FDA's Testing of Cosmetics for Arsenic, Cadmium, Chromium, Cobalt, Lead, Mercury, and Nickel Content," December 2016, available at http://www.fda.gov/Cosmetics/ProductsIngredients/PotentialContaminants/ucm452836.htm.

8. Carrington, C. D., and Bolger, P. M., "An assessment of the hazards of lead in food," Regulatory Toxicology and Pharmacology, vol. 16, pp. 265-272, 1992.

9. Loretz, L. J., Api, A. M., Barraj, L. M., Burdick, J., Dressler, W. E., Gettings, S. D., Han Hsu, H., Pan, Y. H. L., Re, T. A., Renskers, K. J., Rothenstein, A.,, Scrafford, C. G., and Sewall, C., "Exposure data for cosmetic products: lipstick, body lotion, and face cream," Food and Chemical Toxicology, vol. 43, pp. 279-291, 2005.

10. Centers for Disease Control and Prevention, "National Health and Nutrition Examination Survey," available at http://www.cdc.gov/nchs/nhanes.htm.

11. Bress, W. C., and Bidanset, J. H., "Percutaneous in vivo and in vitro absorption of lead," Veterinary and Human Toxicology, vol. 33, pp. 212-214, 1991.

12. Loretz, L. J., Api, A. M. Api, Babcock, L., Barraj, L. M., Burdick, J., Cater, K. C., Jarrett, G., Mann, S., Pan, Y. H. L., Re, T. A., Renskers, K. J., and Scrafford, C. G., "Exposure data for cosmetic products: Facial cleanser, hair conditioner, and eye shadow," Food and Chemical Toxicology, vol. 46, pp. 1516–1524, 2008.

13. El Edelbi, R., Lindemalm, S., and Eksborg, S., "Estimation of body surface area in various childhood ages – validation of the Mosteller formula," Acta Pædiatrica, vol. 101, pp. 540-544, 2012.

14. Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry, "Toxicological Profile for Lead," available at http://www.atsdr.cdc.gov/ToxProfiles/tp13.pdf.

Guidance for Industry

Part 11, Electronic Records; Electronic Signatures — Scope and Application

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

August 2003
Pharmaceutical CGMPs

Guidance for Industry

Part 11, Electronic Records; Electronic Signatures — Scope and Application

Division of Drug Information, HFD-240
Center for Drug Evaluation and Research (CDER)
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research (CBER)
http://www.fda.gov/cber/guidelines.htm
Phone: the Voice Information System at 800-835-4709 or 301-827-1800
or
Communications Staff (HFV-12),
Center for Veterinary Medicine (CVM)
(Tel) 301-594-1755
http://www.fda.gov/cvm/guidance/guidance.html
or
Division of Small Manufacturers Assistance (HFZ-220)
http://www.fda.gov/cdrh/ggpmain.html
Manufacturers Assistance Phone Number: 800.638.2041 or 301.443.6597
Internt'l Staff Phone: 301.827.3993
or
Center for Food Safety and Applied Nutrition (CFSAN)
http://www.cfsan.fda.gov/~dms/guidance.html.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

August 2003
Pharmaceutical CGMPs

TABLE OF CONTENTS

Guidance for Industry[1]
Part 11, Electronic Records; Electronic Signatures — Scope and Application

I. INTRODUCTION

This guidance is intended to describe the Food and Drug Administration's (FDA's) current thinking regarding the scope and application of part 11 of Title 21 of the Code of Federal Regulations; Electronic Records; Electronic Signatures (21 CFR Part 11).[2]

This document provides guidance to persons who, in fulfillment of a requirement in a statute or another part of FDA's regulations to maintain records or submit information to FDA,[3] have chosen to maintain the records or submit designated information electronically and, as a result, have become subject to part 11. Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations. Part 11 also applies to electronic records submitted to the Agency under the Federal Food, Drug, and Cosmetic Act (the Act) and the Public Health Service Act (the PHS Act), even if such records are not specifically identified in Agency regulations (§ 11.1). The underlying requirements set forth in the Act, PHS Act, and FDA regulations (other than part 11) are referred to in this guidance document as *predicate rules.*

[1] This guidance has been prepared by the Office of Compliance in the Center for Drug Evaluation and Research (CDER) in consultation with the other Agency centers and the Office of Regulatory Affairs at the Food and Drug Administration.

[2] 62 FR 13430

[3] These requirements include, for example, certain provisions of the Current Good Manufacturing Practice regulations (21 CFR Part 211), the Quality System regulation (21 CFR Part 820), and the Good Laboratory Practice for Nonclinical Laboratory Studies regulations (21 CFR Part 58).

As an outgrowth of its current good manufacturing practice (CGMP) initiative for human and animal drugs and biologics,[4] FDA is re-examining part 11 as it applies to all FDA regulated products. We anticipate initiating rulemaking to change part 11 as a result of that re-examination. This guidance explains that we will narrowly interpret the scope of part 11. While the re-examination of part 11 is under way, we intend to exercise enforcement discretion with respect to certain part 11 requirements. That is, we do not intend to take enforcement action to enforce compliance with the validation, audit trail, record retention, and record copying requirements of part 11 as explained in this guidance. However, records must still be maintained or submitted in accordance with the underlying predicate rules, and the Agency can take regulatory action for noncompliance with such predicate rules.

In addition, we intend to exercise enforcement discretion and do not intend to take (or recommend) action to enforce any part 11 requirements with regard to systems that were operational before August 20, 1997, the effective date of part 11 (commonly known as legacy systems) under the circumstances described in section III.C.3 of this guidance.

Note that part 11 remains in effect and that this exercise of enforcement discretion applies only as identified in this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In March of 1997, FDA issued final part 11 regulations that provide criteria for acceptance by FDA, under certain circumstances, of electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper. These regulations, which apply to all FDA program areas, were intended to permit the widest possible use of electronic technology, compatible with FDA's responsibility to protect the public health.

After part 11 became effective in August 1997, significant discussions ensued among industry, contractors, and the Agency concerning the interpretation and implementation of the regulations. FDA has (1) spoken about part 11 at many conferences and met numerous times with an industry coalition and other interested parties in an effort to hear more about potential part 11 issues; (2) published a compliance policy guide, CPG 7153.17: Enforcement Policy: 21 CFR Part 11; Electronic Records; Electronic Signatures; and (3) published numerous draft guidance documents including the following:

[4] See *Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach* at www.fda.gov/oc/guidance/gmp.html.

- *21 CFR Part 11; Electronic Records; Electronic Signatures, Validation*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Glossary of Terms*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Time Stamps*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Maintenance of Electronic Records*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records*

Throughout all of these communications, concerns have been raised that some interpretations of the part 11 requirements would (1) unnecessarily restrict the use of electronic technology in a manner that is inconsistent with FDA's stated intent in issuing the rule, (2) significantly increase the costs of compliance to an extent that was not contemplated at the time the rule was drafted, and (3) discourage innovation and technological advances without providing a significant public health benefit. These concerns have been raised particularly in the areas of part 11 requirements for validation, audit trails, record retention, record copying, and legacy systems.

As a result of these concerns, we decided to review the part 11 documents and related issues, particularly in light of the Agency's CGMP initiative. In the *Federal Register* of February 4, 2003 (68 FR 5645), we announced the withdrawal of the draft guidance for industry, *21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records*. We had decided we wanted to minimize industry time spent reviewing and commenting on the draft guidance when that draft guidance may no longer represent our approach under the CGMP initiative. Then, in the *Federal Register* of February 25, 2003 (68 FR 8775), we announced the withdrawal of the part 11 draft guidance documents on validation, glossary of terms, time stamps,[5] maintenance of electronic records, and CPG 7153.17. We received valuable public comments on these draft guidances, and we plan to use that information to help with future decision-making with respect to part 11. We do not intend to re-issue these draft guidance documents or the CPG.

We are now re-examining part 11, and we anticipate initiating rulemaking to revise provisions of that regulation. To avoid unnecessary resource expenditures to comply with part 11 requirements, we are issuing this guidance to describe how we intend to exercise enforcement discretion with regard to certain part 11 requirements during the re-examination of part 11. As mentioned previously, part 11 remains in effect during this re-examination period.

III. DISCUSSION

A. Overall Approach to Part 11 Requirements

[5] Although we withdrew the draft guidance on time stamps, our current thinking has not changed in that when using time stamps for systems that span different time zones, we do not expect you to record the signer's local time. When using time stamps, they should be implemented with a clear understanding of the time zone reference used. In such instances, system documentation should explain time zone references as well as zone acronyms or other naming conventions.

As described in more detail below, the approach outlined in this guidance is based on three main elements:

- Part 11 will be interpreted narrowly; we are now clarifying that fewer records will be considered subject to part 11.
- For those records that remain subject to part 11, we intend to exercise enforcement discretion with regard to part 11 requirements for validation, audit trails, record retention, and record copying in the manner described in this guidance and with regard to all part 11 requirements for systems that were operational before the effective date of part 11 (also known as legacy systems).
- We will enforce all predicate rule requirements, including predicate rule record and recordkeeping requirements.

It is important to note that FDA's exercise of enforcement discretion as described in this guidance is limited to specified part 11 requirements (setting aside legacy systems, as to which the extent of enforcement discretion, under certain circumstances, will be more broad). We intend to enforce all other provisions of part 11 including, but not limited to, certain controls for closed systems in § 11.10. For example, we intend to enforce provisions related to the following controls and requirements:

- limiting system access to authorized individuals
- use of operational system checks
- use of authority checks
- use of device checks
- determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
- establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
- appropriate controls over systems documentation
- controls for open systems corresponding to controls for closed systems bulleted above (§ 11.30)
- requirements related to electronic signatures (e.g., §§ 11.50, 11.70, 11.100, 11.200, and 11.300)

We expect continued compliance with these provisions, and we will continue to enforce them. Furthermore, persons must comply with applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with the predicate rules.

B. Details of Approach – Scope of Part 11

1. Narrow Interpretation of Scope

We understand that there is some confusion about the scope of part 11. Some have understood the scope of part 11 to be very broad. We believe that some of those broad interpretations could

lead to unnecessary controls and costs and could discourage innovation and technological advances without providing added benefit to the public health. As a result, we want to clarify that the Agency intends to interpret the scope of part 11 narrowly.

Under the narrow interpretation of the scope of part 11, with respect to records required to be maintained under predicate rules or submitted to FDA, when persons choose to use records in electronic format in place of paper format, part 11 would apply. On the other hand, when persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable predicate rules and persons rely on the paper records to perform their regulated activities, FDA would generally not consider persons to be "using electronic records in lieu of paper records" under §§ 11.2(a) and 11.2(b). In these instances, the use of computer systems in the generation of paper records would not trigger part 11.

2. Definition of Part 11 Records

Under this narrow interpretation, FDA considers part 11 to be applicable to the following records or signatures in electronic format (part 11 records or signatures):

- Records that are required to be maintained under predicate rule requirements and that are maintained in electronic format *in place of paper format*. On the other hand, records (and any associated signatures) that are not required to be retained under predicate rules, but that are nonetheless maintained in electronic format, are not part 11 records.

  We recommend that you determine, based on the predicate rules, whether specific records are part 11 records. We recommend that you document such decisions.

- Records that are required to be maintained under predicate rules, that are maintained in electronic format *in addition to paper format*, and that *are relied on to perform regulated activities*.

  In some cases, actual business practices may dictate whether you are *using* electronic records instead of paper records under § 11.2(a). For example, if a record is required to be maintained under a predicate rule and you use a computer to generate a paper printout of the electronic records, but you nonetheless rely on the electronic record to perform regulated activities, the Agency may consider you to be *using* the electronic record instead of the paper record. That is, the Agency may take your business practices into account in determining whether part 11 applies.

  Accordingly, we recommend that, for each record required to be maintained under predicate rules, you determine in advance whether you plan to rely on the electronic record or paper record to perform regulated activities. We recommend that you document this decision (e.g., in a Standard Operating Procedure (SOP), or specification document).

- Records submitted to FDA, under predicate rules (even if such records are not specifically identified in Agency regulations) in electronic format (assuming the records have been identified in docket number 92S-0251 as the types of submissions the Agency accepts in electronic format). However, a record that is not itself submitted, but is used

in generating a submission, is not a part 11 record unless it is otherwise required to be maintained under a predicate rule and it is maintained in electronic format.

- Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules. Part 11 signatures include electronic signatures that are used, for example, to document the fact that certain events or actions occurred in accordance with the predicate rule (e.g. *approved*, *reviewed*, and *verified*).

C. Approach to Specific Part 11 Requirements

1. Validation

The Agency intends to exercise enforcement discretion regarding specific part 11 requirements for validation of computerized systems (§ 11.10(a) and corresponding requirements in § 11.30). Although persons must still comply with all applicable predicate rule requirements for validation (e.g., 21 CFR 820.70(i)), this guidance should not be read to impose any additional requirements for validation.

We suggest that your decision to validate computerized systems, and the extent of the validation, take into account the impact the systems have on your ability to meet predicate rule requirements. You should also consider the impact those systems might have on the accuracy, reliability, integrity, availability, and authenticity of required records and signatures. Even if there is no predicate rule requirement to validate a system, in some instances it may still be important to validate the system.

We recommend that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity. For instance, validation would not be important for a word processor used only to generate SOPs.

For further guidance on validation of computerized systems, see FDA's guidance for industry and FDA staff *General Principles of Software Validation* and also industry guidance such as the *GAMP 4 Guide* (See References).

2. Audit Trail

The Agency intends to exercise enforcement discretion regarding specific part 11 requirements related to computer-generated, time-stamped audit trails (§ 11.10 (e), (k)(2) and any corresponding requirement in §11.30). Persons must still comply with all applicable predicate rule requirements related to documentation of, for example, date (e.g., § 58.130(e)), time, or sequencing of events, as well as any requirements for ensuring that changes to records do not obscure previous entries.

Even if there are no predicate rule requirements to document, for example, date, time, or sequence of events in a particular instance, it may nonetheless be important to have audit trails or other physical, logical, or procedural security measures in place to ensure the trustworthiness and

reliability of the records.[6] We recommend that you base your decision on whether to apply audit trails, or other appropriate measures, on the need to comply with predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on product quality and safety and record integrity. We suggest that you apply appropriate controls based on such an assessment. Audit trails can be particularly appropriate when users are expected to create, modify, or delete regulated records during normal operation.

3. Legacy Systems[7]

The Agency intends to exercise enforcement discretion with respect to all part 11 requirements for systems that otherwise were operational prior to August 20, 1997, the effective date of part 11, under the circumstances specified below.

This means that the Agency does not intend to take enforcement action to enforce compliance with any part 11 requirements if all the following criteria are met for a specific system:

- The system was operational before the effective date.
- The system met all applicable predicate rule requirements before the effective date.
- The system currently meets all applicable predicate rule requirements.
- You have documented evidence and justification that the system is fit for its intended use (including having an acceptable level of record security and integrity, if applicable).

If a system has been changed since August 20, 1997, and if the changes would prevent the system from meeting predicate rule requirements, Part 11 controls should be applied to Part 11 records and signatures pursuant to the enforcement policy expressed in this guidance.

4. Copies of Records

The Agency intends to exercise enforcement discretion with regard to specific part 11 requirements for generating copies of records (§ 11.10 (b) and any corresponding requirement in §11.30). You should provide an investigator with reasonable and useful access to records during an inspection. All records held by you are subject to inspection in accordance with predicate rules (e.g., §§ 211.180(c), (d), and 108.35(c)(3)(ii)).

We recommend that you supply copies of electronic records by:

- Producing copies of records held in common portable formats when records are maintained in these formats
- Using established automated conversion or export methods, where available, to make copies in a more common format (examples of such formats include, but are not limited to, PDF, XML, or SGML)

[6] Various guidance documents on information security are available (see References).

[7] In this guidance document, we use the term *legacy system* to describe systems already in operation before the effective date of part 11.

In each case, we recommend that the copying process used produces copies that preserve the content and meaning of the record. If you have the ability to search, sort, or trend part 11 records, copies given to the Agency should provide the same capability if it is reasonable and technically feasible. You should allow inspection, review, and copying of records in a human readable form at your site using your hardware and following your established procedures and techniques for accessing records.

5. Record Retention

The Agency intends to exercise enforcement discretion with regard to the part 11 requirements for the protection of records to enable their accurate and ready retrieval throughout the records retention period (§ 11.10 (c) and any corresponding requirement in §11.30). Persons must still comply with all applicable predicate rule requirements for record retention and availability (e.g., §§ 211.180(c),(d), 108.25(g), and 108.35(h)).

We suggest that your decision on how to maintain records be based on predicate rule requirements and that you base your decision on a justified and documented risk assessment and a determination of the value of the records over time.

FDA does not intend to object if you decide to archive required records in electronic format to nonelectronic media such as microfilm, microfiche, and paper, or to a standard electronic file format (examples of such formats include, but are not limited to, PDF, XML, or SGML). Persons must still comply with all predicate rule requirements, and the records themselves and any copies of the required records should preserve their content and meaning. As long as predicate rule requirements are fully satisfied and the content and meaning of the records are preserved and archived, you can delete the electronic version of the records. In addition, paper and electronic record and signature components can co-exist (i.e., a hybrid[8] situation) as long as predicate rule requirements are met and the content and meaning of those records are preserved.

[8] Examples of hybrid situations include combinations of paper records (or other nonelectronic media) and electronic records, paper records and electronic signatures, or handwritten signatures executed to electronic records.

IV. REFERENCES

Food and Drug Administration References

1. *Glossary of Computerized System and Software Development Terminolo*gy (Division of Field Investigations, Office of Regional Operations, Office of Regulatory Affairs, FDA 1995) (http://www. fda.gov/ora/inspect_ref/igs/gloss.html)

2. *General Principles of Software Validation; Final Guidance for Industry and FDA Staff* (FDA, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research, 2002) (http://www.fda.gov/cdrh/comp/guidance/938.html)

3. *Guidance for Industry, FDA Reviewers, and Compliance on Off-The-Shelf Software Use in Medical Devices* (FDA, Center for Devices and Radiological Health, 1999) (http://www.fda.gov/cdrh/ode/guidance/585.html)

4. *Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach* (FDA 2002) (http://www.fda.gov/oc/guidance/gmp.html)

Industry References

1. *The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems, GAMP 4* (ISPE/GAMP Forum, 2001) (http://www.ispe.org/gamp/)

2. ISO/IEC 17799:2000 (BS 7799:2000) Information technology – Code of practice for information security management (ISO/IEC, 2000)

3. ISO 14971:2002 Medical Devices- Application of risk management to medical devices (ISO, 2001)

Contains Nonbinding Recommendations

Guidance for Industry
Safety of Nanomaterials in Cosmetic Products

You may submit either electronic or written comments regarding this guidance at any time. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-1130.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

June 2014

Table of Contents

Contains Nonbinding Recommendations

Guidance for Industry[1]

Safety of Nanomaterials in Cosmetic Products

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

I. Introduction

This document provides guidance to industry and other stakeholders (e.g., academia, other regulatory groups) on FDA's current thinking on the safety assessment of nanomaterials in cosmetic products. The guidance document is intended to assist industry and other stakeholders in identifying the potential safety issues of nanomaterials in cosmetic products and developing a framework for evaluating them. This guidance also provides contact information for manufacturers and sponsors who wish to discuss safety considerations regarding the use of specific nanomaterials in cosmetic products with FDA. This guidance is not applicable to other products regulated by FDA, including over-the-counter and prescription drugs and medical devices.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in our guidances means that something is suggested or recommended, but not required.

II. Background

Nanomaterials are used in a variety of FDA-regulated products because of their unique properties, imparting potential advantages to products considered for development. Such materials, due to their nanoscale size, can have chemical, physical, and biological properties that differ from those of their larger counterparts. Such differences may include altered magnetic properties, altered electrical or optical activity, increased structural integrity, or altered chemical or biological activity (Ref. 1). These new or altered properties may affect the performance, quality, safety, and/or effectiveness, if applicable, of a product that incorporates that nanomaterial.

[1] This guidance has been prepared by the Office of Cosmetics and Colors in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

In July of 2007, FDA issued a report prepared by its Nanotechnology Task Force ("Task Force"). The Task Force report presented an assessment of scientific and regulatory considerations relating to the safety and effectiveness of FDA-regulated products containing nanomaterials and made recommendations in light of these considerations (Ref. 2). Specifically, with respect to cosmetic products, the Task Force recommended that we issue guidance describing safety issues that manufacturers should consider to ensure that cosmetic products made with nanomaterials are safe and not adulterated. We are issuing this guidance as part of our ongoing efforts to implement the Task Force recommendations (Ref. 2).

The Task Force also recommended that FDA request submission of data and other information addressing the effects of nanomaterials in those products that are not subject to premarket authorization, such as cosmetic products. On September 8, 2008, FDA held a public meeting to discuss such data and information, along with related scientific and regulatory issues concerning nanotechnology. FDA considered the information obtained at, and subsequent to, the public meeting in developing this guidance. We also considered information provided by the cosmetic industry to the International Cooperation on Cosmetics Regulations (ICCR), publications and information regarding recent advances in nanotechnology, and other authoritative guidance/ reports regarding the safety of nanomaterials (Refs. 3, 4, 5, 6). This guidance also refers to other relevant reports, such as the Organization for Economic Co-operation and Development (OECD) Working Party on Manufactured Nanomaterials "Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials" (Ref. 7), the Scientific Committee on Consumer Safety (SCCS) "Guidance on the Safety Assessment of Nanomaterials in Cosmetics" (Ref. 8), and relevant ICCR reports, such as on the "Currently Available Methods for Characterization of Nanomaterials," and "Principles of Cosmetic Product Safety Assessment." (Refs. 9, 10).

FDA has not established regulatory definitions of "nanotechnology," "nanomaterial," "nanoscale," or other related terms. In June 2014, FDA issued a guidance for industry titled "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology" (Ref. 1). As described in that guidance, at this time, when considering whether an FDA-regulated product involves the application of nanotechnology, FDA will ask: (1) whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm); and (2) whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm). We will apply these considerations broadly to all FDA-regulated products, including cosmetic products.

The application of nanotechnology may result in product attributes that differ from those of conventionally-manufactured products, and thus may merit particular examination. However, we do not categorically judge all products containing nanomaterials or otherwise involving application of nanotechnology as intrinsically benign or harmful. Rather, for

nanotechnology-derived and conventionally-manufactured cosmetic products alike, we consider the characteristics of the finished product and the safety for its intended use. Our consideration of nanotechnology applications in cosmetic products in this document is consistent with the agency guidance (Ref. 1) and with the broader federal guidance on regulatory oversight of emerging technologies (Ref. 11) and nanotechnology (Ref. 12).

III. Discussion

A. General Framework for Assessing the Safety of Nanomaterials in Cosmetic Products

Section 301(a) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 331(a)) prohibits the marketing of adulterated or misbranded cosmetics[2] in interstate commerce. The FD&C Act does not subject cosmetics or cosmetic ingredients (with the exception of color additives) to FDA premarket approval in order to be marketed legally in the United States. Except for color additives and those ingredients that are prohibited or restricted from use in cosmetics by regulation, a manufacturer may use any ingredient in the formulation of a cosmetic provided that the use of the ingredient does not otherwise cause the cosmetic to be adulterated (section 601 of the FD&C Act (21 U.S.C. 361)) or misbranded (section 602 of the FD&C Act (21 U.S.C. 362)).[3]

Cosmetic product manufacturers must ensure that the product is not misbranded or adulterated. The FD&C Act does not give us the authority to require that safety data be submitted to us or to approve a cosmetic product before it is marketed. Nevertheless, manufacturers or distributors are responsible for obtaining all data and information needed to substantiate the safety of their products before introducing them into the marketplace.

In the Federal Register of March 3, 1975 (40 FR 8912 at 8916), we advised that "the safety of a product can be adequately substantiated through (a) reliance on already available toxicological test data on individual ingredients and on product formulations that are similar in composition to the particular cosmetic, and (b) performance of any additional toxicological and other tests that are appropriate in light of such existing data and information. Although satisfactory toxicological data may exist for each ingredient of a cosmetic product, it will still be necessary to conduct some toxicological testing with the complete formulation to assure adequately the safety of the finished cosmetic."

We believe that these general principles are applicable to the safety substantiation of cosmetic products whether they contain nanomaterials or conventionally manufactured

[2] The FD&C Act defines cosmetics by their intended use as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness or altering the appearance, and articles intended for use as a component of any such articles; except that such term shall not include soap" (section 201(i) of the FD&C Act).

[3] The name of each ingredient must be declared on the label of the cosmetic product, as required by 21 CFR 701.3.

ingredients. In applying these principles, however, it may be important to give particular consideration to the fact that a material at nanoscale may show changes in, or have novel, physicochemical properties, behaviors, and/or effects that could be different from a larger scale material with the same chemical composition (Refs. 2, 8).

For example, the small particle size of a nanomaterial has the potential to alter the distribution and bioavailability of that material compared to a larger scale material with the same chemical composition. The small size leads to increased surface area relative to the mass of the particle, which could result in increased biological interactions. In addition, the uptake, absorption, and biodistribution of the material may be altered, leading to potential systemic exposure (Refs. 5, 8).

In some cases, the traditional testing methods that have been used to determine the safety of cosmetic ingredients and finished products may not be fully applicable due to a nanomaterial's distinctive properties and behavior. Such distinctive physicochemical characteristics or biological interactions may affect the results or interpretation of results obtained from traditional toxicology testing, which form an integral part of safety substantiation. In Section III.B of this document, we highlight key scientific considerations relevant to the assessment of the safety of nanomaterials used in cosmetic products.

If you wish to use a nanomaterial in a cosmetic product, either a new material or an altered version of an already marketed ingredient, we encourage you to meet with us to discuss the test methods and data that might help substantiate the product's safety, including short-term toxicity and long-term toxicity data, as appropriate. We encourage you to contact us to discuss any aspect of the safety assessment of cosmetic ingredients or finished products.

B. Points to Consider in Assessing the Safety of Nanomaterials in Cosmetic Products

We consider the current framework for safety assessment sufficiently robust and flexible to be appropriate for a variety of materials, including products containing nanomaterials. Just as the traditional safety assessment includes material characterization and toxicology considerations, safety evaluations of cosmetic products containing nanomaterials should also take these considerations into account. As noted in section III.A, nanomaterials may exhibit new or altered physicochemical properties that may affect biological interactions, which may raise questions about the safety of the product containing nanomaterials. Any such unique properties or biological effects of nanomaterials should be identified and appropriately addressed during safety evaluations.

With respect to nanomaterial characterization, safety should be assessed through fully describing the nanomaterial and evaluating a wide range of physical and chemical properties, as well as through the assessment of impurities, if present. The toxicology and absorption, distribution, metabolism, and excretion considerations for nanomaterials in cosmetic products can be informed by addressing the routes of exposure, the uptake and

absorption, and toxicity testing. In addition, any distinctive properties and biological behavior of nanomaterials should be considered in determining the suitability of traditional testing methods for toxicity testing of cosmetic products containing nanomaterials. As needed, traditional toxicity testing methods should be modified or new methods developed to address: (1) the key chemical and physical properties that may affect the toxicity profile of nanomaterials and (2) the effects of those properties on the function of the cosmetic formulation. The toxicological testing should include consideration of toxicity of both the ingredients and impurities; dosimetry for *in vitro* and *in vivo* toxicology studies, if needed; clinical testing, if warranted; and toxicokinetics and toxicodynamics. The overall package of data and information should substantiate the safety of the product under the intended conditions of use. These considerations are discussed in greater detail in sections III.B.1 and III.B.2 below.

1. Nanomaterial Characterization

Nanomaterials vary widely in composition, morphology, and other characteristics and cannot be considered a uniform group of substances. These substances may have physical, chemical, or biological properties that are different from those of larger scale material with the same chemical composition. As stated earlier, such differences may include altered magnetic properties, altered electrical or optical activity, increased structural integrity, or altered chemical or biological activity (Ref. 6).

As discussed in the FDA Task Force report, studies indicate that various attributes of a particular nanoscale material, including increased surface-area-to-volume ratio, morphology, surface features, and charge, can affect the distribution of that material in the body and that material's interaction with biological systems (Ref. 2, 8). Therefore, thorough characterization of nanomaterials can form an integral part of the safety assessment. This would include proper identification of the chemical composition as well as impurities, structure, and configuration of the nanomaterial(s) used in the cosmetic product. In addition, characterization of the nanomaterial(s) as present in the raw material, formulation, test media, and in the relevant biological environment for toxicological testing should be considered to help determine potential biological interactions and effects (Ref. 8). In addition, stability of the nanomaterial under testing conditions and in a formulation under intended conditions of use should be determined.

a. Physicochemical Properties

As with any cosmetic ingredient, the nanomaterial should be fully described, including:

- the nanomaterial name,
- the Chemical Abstracts Service (CAS) number,
- the structural formula,
- the elemental and molecular composition including:

- the degree of purity, and
- any known impurities or additives.

A thorough understanding of the details of the manufacturing process will help identify residual additives and impurities, as well as certain other physical and chemical properties. A wide range of physical and chemical properties should be evaluated to help determine if a substance produced with nanotechnology is safe for the proposed use (Refs. 7, 13, 14, 15). Proper characterization should include, as appropriate:

- measurement of particle size and distribution,
- aggregation and agglomeration characteristics,
- surface chemistry, including:
  - zeta potential/surface charge,
  - surface coating,
  - functionalization, and
  - catalytic activity
- morphology including:
  - shape,
  - surface area,
  - surface topology, and
  - crystallinity
- solubility,
- density,
- stability, and
- porosity.

Although a wide range of analytical techniques are available for measurement of physicochemical properties of materials (Refs. 8, 9, 16), many of these methods have not been validated for the evaluation of nanomaterials in cosmetic products. Therefore, appropriate analytical methods suitable for the specific nanomaterial and the cosmetic product formulation should be chosen, and results obtained from such tests appropriately interpreted and reported for adequate characterization of the material.

b. Impurities

As with any cosmetic ingredient, a change in the starting material used to prepare a formulation will likely result in altered composition of the final product, which may result in different impurities. Variables such as altered purity or changes in the starting material should be considered. A manufacturer should assess the identity and quantity of impurities and how they may affect the overall safety of the end product.

It is also important to understand how the nanomaterial is manufactured. Nanoscale impurities may arise from the manufacturing process. Changes in the manufacturing

process, including use of different solvents, time/temperature conditions and changes to the starting chemicals (*e.g.*, alternative starting materials, different purity levels or different concentrations of the chemicals used in the process) may change the types and/or quantities of impurities in the final product. Additional agents, such as dispersing agents and surface modifiers, are often used in the manufacture of nanomaterials. These additional agents and impurities should be considered in the safety substantiation for nanomaterials in cosmetic products.

2. Toxicology Considerations

The appropriateness of toxicological testing depends on the intended use, exposure levels, and degree of concern for potential toxicity of an ingredient or formulation. In determining what toxicological testing may be appropriate, manufacturers should consider each ingredient's chemical structure and composition, and physicochemical properties, purity/impurities, agglomeration and size distribution, stability, conditions of exposure, uptake and absorption, bioavailability, toxicity, and any other qualities that may affect the safety of the product for its intended use. Manufacturers should address both short-term and long-term toxicity of nanomaterials (Ref. 8), and consider the need to evaluate the possibility of ingredient-ingredient interactions or ingredient-packaging interactions.

Where traditional toxicity test methods are used, manufacturers should consider the applicability of the test methods and, as needed, modify them with respect to such factors as appropriate solvents and dosing formulations, solubility, agglomeration and aggregation of particles, and stability conditions associated with the cosmetic product containing nanomaterials (Refs. 2, 17, 18). For example, whether a nanomaterial is soluble, insoluble, or partially-soluble may affect the suitability of a traditional toxicity test method. Some traditional *in vivo* test methods may be suitable for only soluble nanomaterials (Ref. 17). Some traditional *in vitro* and *in vivo* test methods may need to be adjusted for testing insoluble or partially-soluble nanomaterials (Refs. 7, 18). These considerations are important because nanoparticles tend to stick to each other to form larger agglomerates/aggregates that may be insoluble. Therefore, in a dosing or test medium, nanomaterials may be present as a nano-dispersion rather than in solution (Refs. 7, 18). Agglomeration and aggregation of particles is another factor that may affect the suitability of traditional toxicity testing methods, and manufacturers should ensure that testing appropriately reflects the range of free particles and any aggregates or aggolomerates found in the cosmetic product formulation. Toxicological testing may need to be conducted separately on the free nanoparticles and the agglomerated/aggregated nanoparticles because they will likely have different chemical and biological properties. Due to their high surface energy, nanomaterials may also interact with the testing medium or bind to different substances, including proteins, in the test medium, resulting in an altered biological activity (Refs. 8, 19, 20, 21). Thus, manufacturers should consider and make necessary adjustments to traditional toxicity testing methods, taking into account the specific characteristics of the nanomaterial as it is intended to be used in the cosmetic product. In instances where traditional toxicity testing methods cannot be satisfactorily modified, FDA recommends developing new methods to adequately assess the toxicity of the nanomaterial in the cosmetic product and ensure the product is safe.

It is also important to mention that the dose metrics currently used for toxicological testing of conventionally manufactured chemicals (measured and expressed in mass, volume or number of particles such as mg/kg, or mg/L) may not be appropriate for nanomaterials because of their large surface area per particle mass or volume (Refs. 5, 8). In addition to weight/volume metrics, evaluations of the safety of nanomaterials should also consider alternative metrics, such as weight/volume concentration, particle number concentration and surface area, until suitable parameters for dose metrics become available.

a. Routes of Exposure

The safety of an ingredient is based in part on the potential for exposure and the relevant routes of exposure that are determined by its intended use and its application. Although most cosmetic products are applied directly to the skin, some products may be applied by spray presenting the possibility of inhalation exposure. Additionally, some cosmetic products are applied in an area where there is the possibility of oral exposure. Additionally, systemic absorption can result from dermal, inhalation, ocular and oral exposures (Refs. 22, 23). Therefore, for nanomaterials, the dose to the primary exposure organs as well as the dose to any secondary target organs should be considered in developing or modifying toxicological testing methods and for evaluating the test data (Ref. 5).

b. Uptake and Absorption

As stated above, some nanomaterials have unique physicochemical properties that may alter the potential toxicity of a compound (e.g. reduction in particle size could increase the ability for the compound to be absorbed). Therefore, the safety assessment should address whether there will be an increase in uptake, absorption, transport into cells, and transport across barriers (e.g. blood-brain barrier) or altered bioavailability or biological half-life. For example, there may be an increase in the dose delivered to sensitive tissues due to the increased ability of the nanomaterial to pass through the blood-brain barrier (Ref. 24).

Nanomaterials used in cosmetic products can be divided into two groups: (1) soluble and/or biodegradable nanoparticles, which disintegrate into their molecular components (e.g. some liposomes and nanoemulsions) upon application to skin and thus may not raise safety questions, and (2) insoluble, sufficiently stable and/or biopersistent nanoparticles (e.g. titanium dioxide (TiO_2), fullerenes, and quantum dots). Some insoluble, partially-soluble or sufficiently stable nanomaterials, particularly those in the lower nanoscale range and with certain surface characteristics, may be able to cross biological membrane barriers (Ref. 25) and may have harmful effects due to the potential interaction with organs and cellular compartments. Thus, when there is evidence of systemic exposure to nanomaterials, manufacturers should consider including absorption, distribution, metabolism, and excretion (ADME) parameters in safety assessments of the nanomaterial in the cosmetic product (Ref. 8).

For exposure via dermal absorption, studies should be conducted with both intact skin and impaired skin (e.g. sunburned, atopic, eczematous, psoriatic, or systematically damaged skin)

to address the possibility of an increased rate of penetration and ability of the ingredient to become systemically absorbed. The passive transport of many nanomaterials may not occur through intact skin, but there is an increased probability for entry of nanomaterials through skin with an impaired barrier layer (Refs. 26, 27). A variety of techniques used to study and quantify skin penetration of chemicals are discussed in the literature (Refs. 28, 29). We recognize that there are limitations to using impaired skin models for conducting dermal absorption studies as there is currently no standard or established method(s). We encourage manufacturers to develop appropriate impaired skin models for dermal absorption studies.

The use of aerosolized cosmetic products can also result in exposure to nanomaterials via the respiratory tract. The deposition of nanomaterials in the respiratory system depends on their aerosol properties and interactions with respiratory epithelium. The soluble nanoparticles may be dissolved, metabolized and transported to other organs and blood whereas the insoluble nanoparticles may be either retained in the airways and result in pulmonary effects or swallowed by coughing and cleared. As discussed earlier, the physical characteristics, including surface properties of nanomaterials, are important factors that warrant careful attention, particularly for inhaled nanoscale particles. Studies have indicated that decreasing the size of particles and increasing the surface area can result in potential adverse effects not only in the respiratory system, but also in the heart and blood vessels, the central nervous system, and the immune system (Ref. 30).

Exposure via the oral route is generally limited to those products that are introduced into or applied near the mouth (e.g., mouthwash, lipsticks). Limited evidence suggests that the uptake of nanomaterials and systemic absorption depends on their size, surface charge, and surface ligand modification (Ref. 30). Additional studies have indicated that nanomaterials have limited uptake in the gastrointestinal tract, but the translocation to certain regions of the intestinal barrier can be substantially increased (Refs. 31, 32).

Therefore, we recommend that the safety assessment process for nanomaterials include the issues of toxicokinetics and toxicodynamics with reference to different exposure routes.

c. Toxicity Testing

The initial step in the evaluation of the safety assessment of cosmetic products is to conduct toxicity testing based on a toxicological profile of the ingredients and their routes of exposure. There are several guidelines (Refs. 4, 33, 34) for conducting toxicity testing (tiered testing strategy) of chemicals that can be used as a starting point in evaluating toxicity of nanomaterial ingredients. Consistent with the guidelines issued by the Cosmetic, Toiletry and Fragrance Association (CTFA) (Ref. 33) and the Organization for Economic Co-operation and Development (OECD) (Ref. 3), we recommend, at a minimum, testing for acute toxicity, skin irritation, ocular irritation, dermal photoirritation, skin sensitization, mutagenicity/ genotoxicity, repeated dose (21-28 days) toxicity, and subchronic (90 days) toxicity (Ref. 34). We also recommend phototoxicity testing (Ref. 35) for a cosmetic product that is intended to be used on sun-exposed skin. Results obtained from this basic test battery may indicate a need for additional testing. Where available, other relevant data, such as toxicological data on individual ingredients that are

similar in composition to the nanomaterial or data on a larger scale material with the same chemical composition as the nanomaterial, can also be considered.

As stated previously, in designing tests for use with nanomaterials in cosmetics products, manufacturers should consider modifying traditional toxicity testing with respect to such factors as appropriate solvents and dosing formulations, agglomeration of particles, purity and stability conditions, and other variables. New methods may also need to be developed if traditional tests cannot be modified satisfactorily. For example, the Ames test, recommended as part of a battery of genotoxicity testing for conventional chemicals, may not be suitable for insoluble or partially-soluble nanomaterials used in cosmetic products because the bacterial cell wall may create a possible barrier for many nanomaterials (Ref. 36).

Toxicity testing *in vivo* has long been considered indispensable for obtaining information on translocation, biodistribution, accumulation, and clearance (Ref. 37). As mentioned earlier, while conducting *in vivo* toxicity testing for nanomaterials, careful attention should be paid to the issue of dose metrics (mass, volume or number of particles). The manufacturer should consider the surface area and number of particles, as well as mass concentration in the study design of *in vivo* toxicity testing. For *in vivo* studies via the dermal route of administration, the test substance should be applied directly to the skin, and for the oral route of administration, the test substance should be given either by gavage or in the diet. Agglomeration or aggregation characteristics of nanomaterials in the topical vehicle, gavage or feed matrix are other important factors to assess prior to conducting these studies for safety assessment. Additionally, the potential for nanomaterials to penetrate through the skin or be absorbed through the gut and becoming available for biodistribution, should be addressed while estimating the risks associated with the exposure to nanomaterials.

There has been recent emphasis on the development of validated methods for *in vitro* testing of cosmetic products by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the European Center for the Validation of Alternative Methods (ECVAM). The seventh amendment to Directive 2003/15/EC of the European Parliament and of the Council (Ref. 38) instituted a ban on animal testing of cosmetic products in 2004 and a ban on certain animal tests with validated alternatives in March 2009. We recommend validation of *in vitro* methods for safety testing of cosmetic products and ingredients and optimizing these models for nanomaterials, with particular attention being paid to the issues of cytotoxicity and precipitation of insoluble ingredients. Nanomaterials can settle, diffuse, and aggregate differentially according to their size, density, and surface chemistry (Ref. 39). Thus, the assessment of the agglomeration or aggregation of nanomaterials in the media used in the *in vitro* system should be addressed.

Alternative testing methods currently under consideration that can be optimized for a specific nanomaterial and might be useful to help determine ingredient safety include:

1. Reconstructed human skin such as Episkin™ and Epiderm ™ for skin irritation and corrosion testing;

2. Phototoxicity testing via 3T3 NRPT (3T3 fibroblasts neutral red uptake phototoxicity testing) applicable to ultra violet (UV) absorbing substances;
3. Human/pig skin in a diffusion cell for dermal absorption;
4. Bovine Corneal Opacity and Permeability (BCOP) and the Isolated Chicken Eye (ICE) for ocular irritation; and
5. Genotoxicity testing using a battery of recommended tests covering the endpoints of gene mutation, and structural and numerical aberrations. While conducting genotoxicty tests, the nanomaterial's specific properties should be taken into account to understand the mechanism of nanomaterials' genotoxic effects (Ref. 36).

Finally, we note that *in vivo* studies may be more suitable for nanomaterials with limited solubility properties (Ref. 8).

C. Summary of Recommendations

In summary, nanomaterials can have chemical, physical, and biological properties that differ from those of larger scale particles with the same chemical composition, and the use of nanomaterials in cosmetic products may raise questions about the safety of the product for its intended use. As with any cosmetic product that has new or altered properties, data needs and testing methods should be evaluated to address any unique properties and function of the nanomaterials used in the cosmetic products as well as the questions that continue to remain about the applicability of traditional safety testing methods to products that involve nanotechnology. We recommend that the safety assessment for cosmetic products using nanomaterials should address several important factors, including:

- the physicochemical characteristics,
- agglomeration and size distribution of nanomaterials under the conditions of toxicity testing and as expected in the final product,
- impurities,
- potential routes of exposure to the nanomaterials,
- potential for aggregation and agglomeration of nanoparticles in the final product,
- dosimetry for *in vitro* and *in vivo* toxicology studies, and
- *in vitro* and *in vivo* toxicological data on nanomaterial ingredients and their impurities, dermal penetration, potential inhalation, irritation (skin and eye) and sensitization studies, mutagenicity/genotoxicity studies.

We expect that the science surrounding nanomaterials will continue to evolve and be used in the development of new testing methods.

The safety of a cosmetic product should be evaluated by analyzing the physicochemical properties and the relevant toxicological endpoints of each ingredient in relation to the expected exposure resulting from the intended use of the finished product. If you wish to use a nanomaterial in a cosmetic product, either a new material or an altered version of an

already marketed ingredient, we encourage you to meet with us to discuss the test methods and data needed to substantiate the product's safety, including short-term toxicity and other long-term toxicity data, as appropriate. We welcome your questions relating to the use of nanomaterials in cosmetic products.

IV. How to Contact FDA About this Guidance

Contact the Office of Cosmetics and Colors at 240-402-1130 if you have questions or would like to meet with us. You may also contact FDA by email at industry.cosmetics@fda.gov.

V. References

We have placed these references on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You may see them at that location between 9 a.m. and 4 p.m., Monday through Friday. As of June 3rd , 2014 FDA had verified the Web site addresses for the references it makes available as hyperlinks from the Internet copy of this guidance, but FDA is not responsible for any subsequent changes to Non- FDA Web site references after June 23rd , 2014.

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Guidance for Industry on

Complementary and Alternative Medicine Products and Their Regulation by the Food and Drug Administration

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CBER) Sheryl Lard-Whiteford at 301-827-0379, (CDER) Daniel Nguyen at 301-827-8971, (CDRH) Ted Stevens at 301-594-1184, or (CFSAN) Wayne Amchin at 301-827-6739.

U.S. Department of Health and Human Services
Food and Drug Administration

December 2006

Guidance for Industry:

Complementary and Alternative Medicine Products and Their Regulation by the Food and Drug Administration

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Center for Food Safety and Applied Nutrition (CFSAN)

December 2006

Table of Contents

Complementary and Alternative Medicine Products and Their Regulation by the Food and Drug Administration[1]

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Why Are We Issuing This Guidance?

The term "complementary and alternative medicine" (CAM) encompasses a wide array of health care practices, products, and therapies that are distinct from practices, products, and therapies used in "conventional" or "allopathic" medicine. Some forms of CAM, such as traditional Chinese medicine and Ayurvedic medicine, have been practiced for centuries, whereas others, such as electrotherapy, are more recent in origin.

In the United States, the practice of CAM has risen dramatically in recent years. In 1992, Congress established the Office of Unconventional Therapies, which later became the Office of Alternative Medicine (OAM), to explore "unconventional medical practices." In 1998, OAM became the National Center for Complementary and Alternative Medicine (NCCAM). NCCAM is a center within the National Institutes of Health. The Institute of Medicine, in its book entitled, *Complementary and Alternative Medicine in the United States*, stated that more than one-third of American adults reported using some form of CAM and that visits to CAM providers each year exceed those to primary care physicians.[2]

As the practice of CAM has increased in the United States, the Food and Drug Administration ("FDA", "we") has seen increased confusion as to whether certain products used in CAM (which, for convenience, we will refer to as "CAM products") are subject to regulation under the Federal Food, Drug, and Cosmetic Act ("the Act") or Public Health Service Act ("PHS Act"). We have also seen an increase in the number of CAM products imported into the United States. Therefore, we are providing guidance as

[1] This guidance was prepared by the Office of Policy and Planning, Office of the Commissioner, Food and Drug Administration, with assistance from the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, and the Center for Food Safety and Applied Nutrition.

[2] See Institute of Medicine, *Complementary and Alternative Medicine in the United States*, pages 34-35 (2005).

to when a CAM product is subject to the Act or the PHS Act.[3] This guidance makes two fundamental points:

- First, depending on the CAM therapy or practice, a product used in a CAM therapy or practice ***may*** be subject to regulation as a biological product, cosmetic, drug, device, or food (including food additives and dietary supplements) under the Act or the PHS Act. For example, the PHS Act defines "biological product," and the Act defines (among other things):
  - Cosmetic;
  - Device;
  - Dietary supplement;
  - Drug, as well as "new drug" and "new animal drug;"
  - Food; and
  - Food additive.

  These statutory definitions cover some CAM products.
- Second, neither the Act nor the PHS Act exempts CAM products from regulation. This means, for example, if a person decides to produce and sell raw vegetable juice for use in juice therapy to promote optimal health, that product is a food subject to the requirements for foods in the Act and FDA regulations, including the hazard analysis and critical control point (HACCP) system requirements for juices in 21 CFR part 120. If the juice therapy is intended for use as part of a disease treatment regimen instead of for the general wellness, the vegetable juice would also be subject to regulation as a drug under the Act.

We explain these two points in greater detail later in this document.

II. What Is Complementary and Alternative Medicine (CAM)?

NCCAM defines CAM as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine."[4] It interprets "complementary" medicine as being used together with conventional medicine, whereas "alternative" medicine is used in place of conventional medicine.

NCCAM classifies CAM therapies into four categories or "domains." These are:

- Biologically-based practices;
- Energy therapies;

[3] When this guidance mentions a particular CAM therapy, practice, or product, it does so in order to provide background information or to serve as an example or illustration; any mention of a particular CAM therapy, practice, or product should ***not*** be construed as expressing FDA's support for or endorsement of that particular CAM therapy, practice, or product or, unless specified otherwise, as an agency determination that a particular product is safe and effective for its intended uses or is safe for use.

[4] See NCCAM, "Get the FACTS – What Is Complementary and Alternative Medicine (CAM)?" available at http://nccam.nih.gov/health/whatiscam (accessed on November 22, 2005).

- Manipulative and body-based methods; and
- Mind-body medicine.

NCCAM once had a fifth domain, "Alternative medical systems," but now considers "alternative medical systems" (now known as "whole medical systems") to be a separate category rather than another domain because alternative medical systems use practices from the four domains listed above. For purposes of this guidance, we adopt the same domains and "whole medical systems" category that NCCAM uses.

A. What Are "Biologically Based Practices?"

According to NCCAM, the domain called "biologically based practices" includes, but is not limited to, botanicals, animal-derived extracts, vitamins, minerals, fatty acids, amino acids, proteins, prebiotics[5] and probiotics,[6] whole diets, and "functional foods".[7]

Many biologically-based products within this domain are subject to statutory and regulatory requirements under the Act or the PHS Act. The intended use of a product plays a central role in how it is regulated. For example:

- Botanical products, depending on the circumstances, may be regulated as drugs, cosmetics, dietary supplements, or foods.[8] All four types of

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[5] Prebiotics have been defined as nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon (see Gibson, G.R. and Roberfroid, M.B., "Dietary Modulation of the Human Colonic Microbiota: Introducing the Concept of Prebiotics," Journal of Nutrition, 125: 1401-1412 (1995)). Oligosaccharides are commonly used as prebiotics.

[6] "Probiotics" have been defined as live microbial food supplements which beneficially affect the host animal by improving its intestinal microbial balance (see Fuller, R., "Probiotics in Man and Animals," Journal of Applied Bacteriology, 66: 365-378 (1989)) and as live microorganisms which, when consumed in adequate amounts of food, confer a health benefit on the host (see Food and Agriculture Organization and World Health Organization, "Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria" (1-4 October 2001)). For purposes of this document, we will consider probiotics to refer to whole, live microorganisms that are ingested with the intention of providing a health benefit (such as supporting digestion and nutrient adsorption in the intestine). Our Center for Food Safety and Applied Nutrition, simply refers to such bacteria as "live microorganisms."

"Probiotics" are not defined as a regulatory product category under the Act or the PHS Act, and products that may be considered to be "probiotics" may be foods or drugs under the Act, depending on the intended use of the product.

[7] See NCCAM, "BACKGROUNDER: Biologically Based Practices: An Overview" (October 2004), at page 1 (available at http://nccam.nih.gov/health/backgrounds/biobasedprac.pdf) (accessed on November 22, 2005)). NCCAM interprets "functional foods" as "components of the usual diet that may have biologically active components (e.g., polyphenols, phytoestrogens, fish oils, carotenoids) that may provide health benefits beyond basic nutrition" (id. at page 3). However, "functional foods" are not defined as a regulatory product category, and products that NCCAM would interpret to be "functional foods" would either be foods or drugs to FDA, depending on the claims associated with the product.

[8] Although dietary supplements are a type of food (see section 201(ff) of the Act (last sentence)), for ease of reference, we will use the term "food" to refer to foods other than dietary supplements (e.g., conventional foods, food additives, or GRAS substances intended for use in food) throughout the remainder of this guidance. We may discuss specific types of "foods," such as "food additives," separately

products are subject to the Act. For example, a botanical product intended for use in treating a disease would generally be regulated as a drug; a botanical product taken by mouth, labeled as a dietary supplement, and intended for use to affect the structure or function of the body would generally be regulated as a dietary supplement; a raw or dried botanical intended for use as an ingredient to flavor food would generally be regulated as a food or as a food additive, depending on whether the botanical was generally recognized as safe for its intended use in food; and a lotion containing botanical ingredients and intended for use in moisturizing the skin would generally be regulated as a cosmetic.

- Probiotics may be regulated as dietary supplements, foods, or drugs under the Act, depending on the product's intended use. Other factors may also affect the classification of the product, e.g., whether the product contains a "dietary ingredient" as defined in section 201(ff)(1) of the Act (21 U.S.C. 321(ff)(1)), whether it is represented as a conventional food or as a meal replacement (see section 201(ff)(2)(B) of the Act), and, for probiotics used as ingredients in a conventional food, whether the ingredient is generally recognized as safe for its intended use (see section 201(s) of the Act (21 U.S.C. 321(s)). In addition to any requirements that apply based on the product's classification under the Act, probiotics may also be subject to the PHS Act's provisions concerning the prevention of communicable disease, due to potential disease-causing microorganisms that might be contained in such products. Finally, if a probiotic is a drug under the Act, it may be subject to regulation as a biological product under the PHS Act as well.
- Products that NCCAM would consider to be "functional foods" may be subject to FDA regulation as foods, dietary supplements, or drugs under the Act. As with botanicals and probiotics, the classification of a "functional food" under the Act is based primarily on the product's intended use and may also involve other factors, depending on the elements of the statutory definition of a particular product category.

B. What Is "Energy Medicine?"

NCCAM considers energy medicine to involve energy fields of two types:

- Veritable energy fields, which can be measured and use either mechanical vibrations (such as sound) or electromagnetic forces, including visible light, magnetism, monochromatic radiation (such as laser light), and other light rays; and
- Putative energy fields (or biofields) that have defied measurement to date by reproducible methods. According to NCCAM, therapies involving putative energy fields "are based on the concept that human beings are

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to explain additional statutory or regulatory requirements or concepts, but those products are still "foods" under the Act.

> infused with a subtle form of energy" and therapists "claim that they work with this subtle energy, see it with their own eyes, and use it to effect changes in the physical body and influence health."[9]

In a sense, "conventional" medicine already uses various forms of "energy" medicine. For example, a magnetic resonance imaging (MRI) device uses electromagnetic waves to create images of internal body organs and tissues. As another example, an ultrasound machine uses sound waves to create images of body organs, tissues, and fetuses. Given their intended uses, we regulate these products as medical devices under the Act.

CAM products that use veritable energy fields in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease in man or animals or to affect the structure or any function of the body of man or animals may be medical devices under the Act.[10] Additionally, if the product is electronic and emits radiation, it may be subject to additional requirements to ensure that there is no unnecessary exposure of people to radiation.

CAM products that use putative energy fields in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or animals may be medical devices under the Act. For example, we regulate acupuncture needles as "class II" medical devices.[11]

C. What Are "Manipulative and Body-Based Practices?"

According to NCCAM:

> Under the umbrella of manipulative and body-based practices is a heterogeneous group of CAM interventions and therapies. These include chiropractic and osteopathic manipulation, massage therapy, Tui Na, reflexology, rolfing, Brown technique, Trager bodywork, Alexander technique, Feldenkrais method, and a host of others….
>
> Manipulative and body-based practices focus primarily on the structures and systems of the body, including the bones and joints, the soft tissues, and the circulatory and lymphatic systems….[12]

To the extent that manipulative and body-based practices involve practitioners physically manipulating a patient's body, without using tools or machines, we do not

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[9] See NCCAM, "BACKGROUNDER – Energy Medicine: An Overview (August 2005), at page 1 (available at http://nccam.nih.gov/health/backgrounds/energymed.pdf) (accessed on November 22, 2005).

[10] See section 201(h)(2) and (h)(3) of the Act (21 U.S.C. 321(h)(2) and (h)(3)) (definition of "device").

[11] See 21 CFR 880.5580.

[12] See NCCAM, "BACKGROUNDER: Manipulative and Body-Based Practices: An Overview" (December 2004), at page 1 (available at http://nccam.nih.gov/health/backgrounds/manipulative.pdf) (accessed on November 22, 2005).

believe that such practices are subject to regulation under the Act or the PHS Act. If, however, the manipulative and body-based practices involve the use of equipment (such as massage devices) or the application of a product (such as a lotion, cream, or oil) to the skin or other parts of the body, those products may be subject to regulation under the Act, depending on the nature of the product and its intended use..

D. What Is "Mind-Body Medicine?"

NCCAM describes mind-body medicine as focusing on "the interactions among the brain, mind, body, and behavior, and the powerful ways in which emotional, mental, social, spiritual, and behavioral factors can directly affect health."[13] It states that mind-body medicine "typically focuses on intervention strategies that are thought to promote health, such as relaxation, hypnosis, visual imagery, meditation, yoga, biofeedback, tai chi, qi gong, cognitive-behavioral therapies, group support, autogenic training, and spirituality."[14]

In general, CAM practices in this domain would *not* be subject to our jurisdiction under the Act or the PHS Act. As with the manipulative and body-based practices domain, however, any equipment or other products used as part of the practice of mind-body medicine may be subject to FDA regulation, depending on the nature of the product and its intended use. For example, biofeedback machines intended to help a patient learn to affect body functions, such as muscle activity, are regulated as class II devices.[15]

E. What Are "Whole Medical Systems?"

NCCAM describes whole medical systems as involving "complete systems of theory and practice that have evolved independently from or parallel to allopathic (conventional) medicine."[16] These may reflect individual cultural systems, such as traditional Chinese medicine and Ayurvedic medicine. Some elements common to whole medical systems are a belief that the body has the power to heal itself, and that healing may involve techniques that use the mind, body, and spirit.

Although it is unlikely that a whole medical system itself would be subject to regulation under the Act or the PHS Act, products used as *components* of whole medical systems may be subject to FDA regulation for the reasons described above.

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[13] See NCCAM, "BACKGROUNDER: Mind-Body Medicine: An Overview" (August 2005), at page 1 (available at http://nccam.nih.gov/health/backgrounds/mindbody.pdf) (accessed on November 22, 2005).

[14] Id.

[15] See 21 CFR 882.5050.

[16] See NCCAM, "BACKGROUNDER: Whole Medical Systems: An Overview" (October 2004), at page 1 (available at http://nccam.nih.gov/health/backgrounds/wholemed.pdf) (accessed on November 22, 2005).

III. How Do CAM Domains Relate to Products That We Regulate?

Given the vast array of CAM products, practices, and therapies, it is impractical for us to describe in detail how each one might be subject to regulation under the Act or the PHS Act. Our intent, in part IV of this document, is two-fold:

- To indicate which CAM domains might be subject to regulation under the Act or the PHS Act; and
- To show that neither the Act nor the PHS Act contains any exemption for CAM products. In other words, if a product meets the statutory definition of drug, device, biological product, food, etc., it will be subject to regulation under the Act and/or the PHS Act.

IV. What FDA Authority Might Apply to CAM Products?

A. What Statutory Definitions Might Apply?

To understand how the Act or the PHS Act might apply to CAM products, we begin by understanding the Act's statutory definitions or, in the case of the PHS Act, our authority regarding biological products.

1. "Drug" and "New Drug"

Section 201(g)(1) of the Act (21 U.S.C. 321(g)(1)) defines the term "drug," in relevant part, to mean:

> (A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C).

Section 201(p) of the Act (21 U.S.C. 321(p)) defines the term "new drug" to mean:

> (1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that the drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective[17] for use under the conditions prescribed, recommended, or suggested in

[17] In *Weinberger* v. *Hynson, Westcott and Dunning*, 93 S.Ct. 2469, 2483 (1973), the Supreme Court stated that "general recognition" of effectiveness "requires at least 'substantial evidence' of effectiveness for approval" of a new drug application (NDA). (An NDA is the marketing application for a new drug.)

> the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of use; or
>
> (2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

To illustrate how these definitions might apply, consider an herbal product that is intended to treat arthritis in humans. The herbal product, which would be a "biologically based practice" insofar as CAM domains are concerned, would be a "drug" under section 201(g)(1)(B) of the Act because it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease (arthritis) in man. The same herbal product would also be a "new drug" under section 201(p)(1) of the Act unless it is generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling. "New drug" status triggers the Act's requirements for premarket review and approval by FDA.[18]

A detailed discussion of the Act's drug provisions is beyond the scope of this guidance document. Note, however, that the Act imposes certain requirements (including requirements pertaining to establishment registration and product listing, pre-market approval, labeling, postmarket reporting, and good manufacturing practices) on those who manufacture and distribute drugs. The Act and our drug regulations can be found at our website at http://www.fda.gov/opacom/laws.

2. "Device"

In general, section 201(h) of the Act (21 U.S.C. 321(h)) defines the term "device" as:

> an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory which is –

Section 505(d) of the Act (21 U.S.C. 355(d)) defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations conducted by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." Thus, "general recognition" is a high standard.

[18] Under section 505(a) of the Act (21 U.S.C. 355(a)), "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to [section 505(b) or 505(j) of the Act] is effective with respect to such drug."

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals, and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

To illustrate how a CAM product might be a "device" under the Act, acupuncture is a CAM therapy that seeks to stimulate energy pathways ("meridians") by puncturing, pressing, heating, using electrical current, or using herbal medicines. Fine needles are often used, and these acupuncture needles are "devices" under section 201(h) of the Act because they are intended for use in the cure, mitigation, treatment, or prevention of disease in man or are intended to affect the structure or function of the body of man. We regulate acupuncture needles (see 21 CFR 880.5580), but not the practice of acupuncture itself.

A detailed discussion of the Act's device provisions is beyond the scope of this guidance document. Note, however, that the Act establishes classifications for devices (class I, II, or III) that affect how they are regulated. The Act also imposes certain requirements on those who manufacture devices (including requirements pertaining to establishment registration and product listing, pre-market review, labeling, postmarket reporting, and good manufacturing practices). Certain requirements also apply to device distributors. The Act and our device regulations can be found at our website at www.fda.gov/opacom/laws.

3. "Food"

Section 201(f) of the Act (21 U.S.C. 321(f)) defines the term "food" to mean "articles used for food or drink for man or other animals," chewing gum, and articles used for components of any such article.

To illustrate how a CAM practice might involve "foods," juice therapy uses juice made from vegetables and fruits. Absent any claims that would make the juice subject to the drug definition, the juice would be a "food" under section 201(f) of the Act because it is an article used for food or drink for man.

A detailed discussion of the Act's food provisions is beyond the scope of this guidance document. However, anyone who intends to market CAM products that might be subject to regulation under these provisions should familiarize himself/herself with the Act's requirements for foods, particularly with respect to safety and labeling. The Act and our food regulations can be found at our website at www.fda.gov/opacom/laws.

4. "Food Additive"

Section 201(s) of the Act (21 U.S.C. 321(s)) defines the term "food additive" to mean, in part, "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food….if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use…."[19]

To illustrate how a CAM product might involve "food additives" under section 201(s) of the Act, some CAM practices involve dietary modifications where substances such as botanicals or enzymes are added to foods in the diet. If a manufacturer adds such a substance to a food, the substance may fall within the "food additive" definition at section 201(s) of the Act. A food additive is subject to premarket approval by FDA under section 409 of the Act (21 U.S.C. 348). Food additives that we have not approved or that do not comply with applicable FDA regulations prescribing safe conditions of use are deemed to be unsafe under section 409(a) of the Act, and foods that contain such additives are adulterated under section 402(a)(2)(C) of the Act (21 U.S.C. 342(a)(2)(C)). The Act provides that a substance is exempt from the definition of a food additive and thus, from pre-market approval, if, among other reasons, it is generally recognized as safe (GRAS) by qualified experts under the conditions of intended use. Whether a substance added to a food is considered to be a food additive or is GRAS, any claims associating the substance with the reduction of a disease risk are "health claims" (defined in 21 CFR 101.14(a)(1)) that require premarket review by FDA.[20]

A detailed discussion of the Act's food additive provisions is beyond the scope of this guidance document. However, anyone intending to market CAM products that are or contain substances that might be subject to regulation as food additives should familiarize himself/herself with the Act's food additive requirements. The Act and our food additive regulations can be found at our website at www.fda.gov/opacom/laws.

5. "Dietary Supplement"

Section 201(ff) of the Act (21 U.S.C. 321(ff)) defines the term "dietary supplement" as follows:

The term "dietary supplement" -

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[19] The statutory definition of "food additive" exempts certain substances, such as pesticide chemical residues in or on a raw agricultural commodity or processed food, pesticide chemicals, color additives, dietary ingredients in or intended for use in a dietary supplement (as defined in section 201(ff) of the Act), and new animal drugs.

[20] See 21 CFR 101.70.

(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin;
(B) a mineral;
(C) an herb or other botanical;
(D) an amino acid;
(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);

(2) means a product that

(A) (i) is intended for ingestion in a form described in section 411(c)(1)(B)(i); or
(ii) complies with section 411(c)(1)(B)(ii);
(B) is not represented for use as a conventional food or as a sole item of a meal or the diet; and
(C) is labeled as a dietary supplement; and

(3) does--

(A) include an article that is approved as a new drug under section 505 or licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262) and was, prior to such approval, certification, or license, marketed as a dietary supplement or as a food unless the Secretary has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section 402(f); and
(B) does not include—
(i) an article that is approved as a new drug under section 505, certified as an antibiotic under section 507, or licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262), or
(ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public,

which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the Secretary's discretion, has issued a regulation, under notice and comment, finding that the article would be lawful under this Act.

Except for purposes of section 201(g) [of the Act], a dietary supplement shall be deemed to be a food within the meaning of this Act.

To illustrate how a CAM product might be a "dietary supplement" under section 201(ff) of the Act, consider botanical products used in naturopathy. (Naturopathy is a CAM whole medical system that views disease as a manifestation of alterations in the

processes by which the body heals itself.[21]) For example, naturopathic cranberry tablets might be labeled for use to maintain the health of the urinary tract. In this example, the cranberry tablets generally would be regulated as "dietary supplements" under section 201(ff)(1) of the Act if they were labeled for use to "maintain the health of the urinary tract" rather than "prevent urinary tract infections." The cranberry tablets would be regulated as "drugs" under section 201(g) of the Act if they were labeled for use to "treat urinary tract infections" even if they were labeled as dietary supplements.

A detailed discussion of the Act's dietary supplement provisions is beyond the scope of this guidance document. However, anyone intending to market CAM products that might be subject to regulation as a dietary supplement should familiarize himself/herself with the Act's dietary supplement requirements, particularly with respect to safety and labeling. The Act and our dietary supplement regulations can be found at our website at www.fda.gov/opacom/laws.

6. "Cosmetic"

Section 201(i) of the Act defines the term "cosmetic" to mean "(1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap."

It is possible that certain products used in conjunction with CAM practices may be "cosmetics" under the Act. For example, if a CAM practice involves massage with a moisturizer, the moisturizer could be a "cosmetic" to the extent that it is "rubbed, poured, sprinkled, or sprayed on" the body for beautification or appearance-altering purposes. However, if the moisturizer's intended use is also for the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body, then it may also be subject to regulation as a drug. Other examples of drug/cosmetic combinations are deodorants that are also antiperspirants, moisturizers and makeup marketed with sun-protection claims, and shampoos that also treat dandruff.

The Act does not require premarket approval for cosmetics, but it does prohibit the marketing of adulterated or misbranded cosmetics in interstate commerce. Anyone intending to market CAM products that might be subject to regulation as cosmetics should familiarize himself/herself with the safety and labeling requirements for these products in the Act and our regulations. The Act and our cosmetic regulations can be found at our website at www.fda.gov/opacom/laws.

[21] See NCCAM, "BACKGROUNDER: Whole Medical Systems: An Overview" (October 2004) at pages 3-4.

7. "Biological Product"

Section 351(a)(1) of the PHS Act (42 U.S.C. 262(a)(1)) states, in part, that no person "shall introduce or deliver for introduction into interstate commerce any biological product" unless that product has an effective license and its package is plainly marked with the product's proper name, the name, address, and applicable license number of the biological product's manufacturer, and the product's expiration date. Section 351(a)(2) of the PHS Act gives us the authority to establish requirements for the approval, suspension, and revocation of biological product licenses.

Section 351(i) of the PHS Act defines "biological product" as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition in human beings." The term "virus" captures a broad spectrum of microorganisms that cause an infectious disease and includes, but is not limited to, filterable viruses, bacteria, rickettsia, fungi, and protozoa (see 21 CFR 600.3(h)(1)).

It is conceivable that some "biologically based practices" (as defined by NCCAM) could involve the use of "biological products" as defined by section 351(i) of the PHS Act. For example, the bacteria used in a probiotic product could make the product a "biological product" subject to the PHS Act.

A detailed discussion of biological product regulation under the PHS Act is beyond the scope of this guidance document. Note, however, that in addition to our authority under section 351 of the PHS Act, section 361 of the PHS Act (42 U.S.C. 264) authorizes us to make and enforce regulations "to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession." If a CAM product manufacturer attempted to use a live, disease-causing virus as a component of a CAM product, we could exercise our authority under section 361 of the PHS Act and 21 CFR 1240.30 to take action against the product, in addition to consider the applicability of section 351 of the PHS Act. The PHS Act and FDA's regulations for biological products can be found at our website at www.fda.gov/opacom/laws.

V. Whom Do You Contact For More Information?

For more information about how we regulate drugs, devices, cosmetics, foods (including food additives and dietary supplements), and biological products, visit our website at www.fda.gov. We also have many other guidance documents that present our current thinking on a particular topic.

For more information about products that we regulate, and how they might relate to CAM, please contact:

- For biological products, the Manufacturers Assistance and Technical Training Branch, Office of Communication, Training & Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 1-800-835-4709 or 301-827-1800.

- For cosmetics, the Office of Cosmetics and Colors, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Parkway, College Park, MD 20740, 301-436-1130.

- For devices, the Office of Communication, Education, and Radiation Programs (HFZ-220), Center for Devices and Radiological Health, Food and Drug Administration, 1350 Piccard Drive, Rockville, MD 20850, 1-800-638-2041 or 301-827-3990.

- For dietary supplements, the Division of Dietary Supplement Programs (HFS-810), Office of Nutritional Products, Labeling, and Dietary Supplements, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Parkway, College Park, MD 20740, 301-436-2375.

- For foods and food additives, the Office of Food Additive Safety (HFS-200), Center for Food Safety and Applied Nutrition, Food And Drug Administration, 5100 Paint Branch Parkway, College Park, MD 20740-3835, 301-436-1200

- For human drugs, the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4570 or 1-888-463-6332. You can also send electronic mail inquiries to druginfo@cder.fda.gov.

Contains Nonbinding Recommendations
Draft-Not for Implementation

Guidance for Industry

Cosmetic Good Manufacturing Practices

Draft Guidance

Additional copies are available from:
Office of Cosmetics and Colors, HFS-100
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740
(Tel) 240-402-1130
http://www.fda.gov/CosmeticGuidances

You may submit written comments regarding this guidance at any time. Submit written comments on the guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the title of the guidance document.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

February 12, 1997; revised April 24, 2008 and June 2013

Table of Contents

Guidance for Industry[1]
Cosmetic Good Manufacturing Practices

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

I. Introduction

This document provides guidance to industry and other stakeholders (e.g., consumer interest groups, academia, other regulatory groups) on FDA's current thinking concerning what constitutes Good Manufacturing Practices (GMPs) for cosmetics. It is intended to assist industry and other stakeholders in identifying the standards and issues that can affect the quality of cosmetic products.

This guidance revises the "Cosmetic Good Manufacturing (GMP) Guidelines/Inspection Checklist" by updating it to set forth current practice, and clarify certain topic areas based on recent experience. In addition, as part of an international harmonization effort with the International Cooperation on Cosmetic Regulations (ICCR), FDA (or we) agreed to consider the current International Organization for Standardization (ISO) standard for cosmetic GMPs (ISO 22716:2007) when revising this guidance. We reviewed ISO 22716 and decided to incorporate, modify, or exclude specific aspects of it into this guidance based on our experience.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. Background

The predecessor to this guidance, FDA's "Cosmetic Good Manufacturing Guidelines/Inspection Checklist," was based on documents and information dating before the early 1990's. Much of the material in the predecessor document has become outdated. In addition, there has been a great deal of progress in developing international consensus standards for cosmetics, specifically

[1] This guidance has been prepared by the Office of Cosmetics and Colors in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

ISO 22716 (*Cosmetics – Good Manufacturing Practices (GMP) – Guidelines on Good Manufacturing Practices*. ISO 22716:2007. Geneva, Switzerland:ISO.).

ISO is a non-governmental organization that develops and publishes international consensus standards. In September 2007, the International Cooperation on Cosmetic Regulation (ICCR), the quadrilateral international harmonization group, met in Belgium. During that meeting, the regulators from the United States, Canada, the European Union, and Japan agreed that it would be useful for the cosmetic industry to have a standardized scheme for GMPs that could apply to their jurisdictions. As a result, the regulators from these four jurisdictions agreed to take ISO standards for cosmetic GMPs into consideration when developing or updating guidelines or other measures addressing GMPs (See International Cooperation on Cosmetic Regulation: Outcome of Meeting, September 26-28, 2007). In developing this guidance, FDA has incorporated elements of ISO 22716, as appropriate, and consistent with FDA regulations.

III. Discussion

A. Overview

The Federal Food, Drug and Cosmetic Act (the FD&C Act) prohibits the introduction, or delivery for introduction, into interstate commerce of cosmetics that are adulterated or misbranded (Section 301 of the FD&C Act).

If you manufacture cosmetics, you can reduce the risk of adulterating or misbranding cosmetics by following the GMP recommendations in this guidance. By following these recommendations, you can effectively conduct a self-inspection to rate your operations.

Tampering and other malicious, criminal, or terrorist activity present additional risks that can also have a direct impact on your products' quality. To help minimize these risks to cosmetics under your control, we recommend that you consult a separate FDA guidance document entitled "Guidance for Industry: Cosmetic Processors and Transporters of Cosmetics Security Preventive Measures Guidance."

B. Definitions

We recommend that you refer to the FD&C Act and Title 21 of the Code of Federal Regulations (21 CFR) for definitions of the terms "cosmetic" (Section 201(i) of the FD&C Act) and "tamper-resistant packaging" (21 CFR 700.25). In addition, the following terms apply to this guidance:

Documentation: 1) The supplying of documents or supporting references; use of documentary evidence; 2) the documents or references thus supplied; 3) the collecting, abstracting, and coding of printed or written information for future reference. ("documentation," Webster's New World Dictionary Third College Edition, 1988 ed.).

Good manufacturing practice (GMP): That part of quality assurance aimed at ensuring that products are consistently manufactured to a quality appropriate to their intended use. It is thus concerned with both manufacturing and quality control procedures. (Sharp, John, Good Manufacturing Practice, Philosophy and Applications, Buffalo Grove, IL: Interpharm Press, 1991, pg. 47.).

Internal Audit: Systematic and independent examination made by competent personnel inside the company, the aim of which is to determine whether activities covered by these guidelines and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable for achieving objectives. (*Cosmetics – Good Manufacturing Practices (GMP) – Guidelines on Good Manufacturing Practices*, ISO 22716:2007, Geneva, Switzerland: ISO.).

Standard operating procedure (SOP): Instructions on how to perform tasks and descriptions of the approved or required procedures for accomplishing specific quality assurance objectives. (Garfield. F.M., Klesta, E., and Hirsch, J., eds., Quality Assurance Principles for Analytical Laboratories, 3rd Ed., Gaithersburg, MD: AOAC International, 2000, pg. 26).

C. Specific Guidance for Cosmetics[2]

Documentation

Documentation creates a mechanism that shows how products are manufactured and tested. Documentation should define your organization's processes and capture every aspect of your manufacturing process. Documentation prevents errors of interpretation or loss of information that may result from reliance on verbal communication. Documentation also allows you to trace where any problems may have occurred and to take appropriate corrective action.

Records

Records should be retained in either paper or electronic format. Records should capture in detail the operations, procedures, deviations from procedures, justifications, instructions (including training), specifications, protocols, reports, methods, precautions, corrections and other measures, and other appropriate information related to GMPs.

You should review raw material records to determine if raw material is adequately controlled. These records may include origin, receipt, examination, testing, disposition, and use records.

You should determine whether disposition of rejected materials or returned goods is documented. (For example, reworking operations, returns to suppliers, and disposals).

You should evaluate batch production control records, which should include:

[2] There are no GMP regulations for cosmetics.

- Documentation of all ingredients (name, code, lot number, quantity, etc.) added to the batch
- Documentation of all production steps (for example, processing, handling, transferring, holding, and filling)
- In-process sampling, controlling, and adjusting steps
- Batch and finished product lot or control numbers
- The finished products control status – accepted or rejected

You should evaluate laboratory control records for raw materials, in-process materials, and finished products. These records should include documentation of sampling procedures, test results, and interpretation of the test results (accepts or reject).

You should determine if records are adequate to conduct an effective recall. Initial distribution records identifying the consignee, the product, and the lot or control number should be retained.

You should determine if records are developed in a timely manner after an event occurs.

Buildings and Facilities

You should determine whether the buildings and facilities used for manufacturing are of suitable size, design, and construction, and maintained in a clean and orderly manner. Buildings should provide:

- Space of sufficient size and adequate organization to prevent selection errors (i.e., mix-ups) or cross contamination between consumables, raw materials, intermediate formulations (i.e., in-process materials), and finished products (This applies to containers, closures, labels and labeling materials as well.)
- Adequate filth and pest controls (Examples of filth may include any objectionable matter, contributed by animal contamination such as rodent, insect, or bird matter; or any other objectionable matter contributed by insanitary conditions.)
- Floors, walls, and ceilings constructed of smooth, easily cleanable surfaces
- Adequate lighting and ventilation, and, if necessary for control purposes, screening, filtering, dust, humidity, temperature, and bacteriological controls
- Adequate washing, cleaning, plumbing, toilet, and locker facilities to allow for sanitary operation; cleaning of facilities, equipment, and utensils; and personal cleanliness; and
- Fixtures, ducts, pipes, and drainages installed to prevent condensate or drip contamination

Equipment

You should determine whether equipment and utensils used in processing, holding, transferring and packaging are of appropriate design, size, material and workmanship for the intended purpose to prevent corrosion, accumulation of static material and/or adulteration with lubricants, coolants, dirt, and sanitizing agents. The equipment (for example, utensils, pipework, cosmetic contact surfaces, and balances) should be:

- Maintained in a clean and orderly condition, sanitized at appropriate times, and stored in a manner that protects against splash, dust, and other contaminants
- Constructed to facilitate adjustment, cleaning, and maintenance
- Of suitable size and accuracy for measuring, mixing, and weighing operations
- Calibrated regularly or checked according to an SOP with results documented, where appropriate
- Removed from use if it is defective, does not meet recommended tolerances, or cannot be repaired and calibrated immediately

Personnel

You should determine whether personnel supervising or performing cosmetics manufacturing or control have the education, training, and/or experience to perform their assigned functions. In addition:

- Personnel coming in direct contact with cosmetic raw materials, in-process materials, finished products, or contact surfaces should wear clean clothing appropriate for the duties they perform and necessary protective apparel (for example, uniforms, gloves, safety glasses, and hair restraints).
- Personnel should also maintain adequate personnel cleanliness, and be free from abnormal sources of microbiological contamination (for example, sores and infected wounds)
- Eating food, drinking beverages, or using tobacco should be restricted to appropriate designated areas away from storage and processing areas
- All personnel and visitors should be properly supervised while in the manufacturing facility; and
- Only authorized personnel should be allowed access into production, storage, and product control areas

Raw Materials

You should determine whether raw materials are identified, stored, examined, tested, inventoried, handled, and controlled to ensure they conform to appropriate standards and specifications. In particular, raw materials should be:

- Stored and handled to prevent mistakes (i.e., mix-ups or selection errors), contamination with microorganisms or other chemicals, and degradation from exposure to excessive environmental conditions (e.g., heat, cold, sunlight, moisture, etc.)
- Held in closed containers and stored off the floor
- Maintained in containers that are labeled with the identity, lot number, and control status (release or quarantine)
- Sampled and tested for conformance with specifications and to ensure the absence of filth, microorganisms, and other adulterants prior to processing or usage (Animal and vegetable origin materials and those produced by cold processing methods should be reviewed for filth and/or microorganism contamination.); and
- Properly identified and controlled to prevent the use of materials that fail to meet acceptance specifications

Water

You should determine whether:

- The water used as a cosmetic ingredient is used as-is (i.e., directly from the tap) or if it has been treated before being used (i.e., has it been treated by such means as deionization, distillation, or reverse osmosis)
- There are established procedures for ensuring that the water used as a cosmetic ingredient
    - Is of a defined quality
    - Is not affected by materials used in the water treatment equipment
    - Is being tested or monitored regularly to verify that it meets applicable chemical, physical, and microbiological specifications for quality; and
    - The entire system for supplying water used as a cosmetic ingredient is set up to avoid stagnation and risks of contamination (This system should be routinely cleaned and sanitized according to an appropriate SOP that ensures no biofilm build-up.)

Color Additives

You should determine whether color additives are approved for use in your specific cosmetic products (21 CFR parts 73, 74, and 82). Should an unlisted color additive be an ingredient of the cosmetic, approval of a petition for a new color additive is required pursuant to 21 CFR parts 70 and 71. A summary chart for color additives can be found on FDA's website. Color additives subject to certification must be labeled with the lot number assigned by the Color Certification Branch[3] (21 CFR 70.25(d)) (see exception below[4]).

Prohibited and Restricted Cosmetic Ingredients

Certain ingredients are prohibited from use in cosmetic products marketed in the United States; others have restrictions on their use. Ingredients whose use is prohibited or restricted are listed in the tables below.

In addition to the prohibited and restricted ingredients listed in the following tables, you should check the CFR, specifically 21 CFR part 700, Subpart B, for any additional requirements regarding specific cosmetic products or their ingredients that may have been added to FDA's regulations.

[3] The Color Certification Branch is located in the Office of Cosmetics and Colors in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

[4] Color additives must be labeled with the lot number assigned by the Color Certification Branch, except in the case of any mixture for household use which contains not more than 15 percent of pure color and which is in packages containing not more than 3 ounces there appears on the label, a code number which the manufacturer has identified with the lot number by giving to the FDA written notice that such code number will be used in lieu of the lot number (21 CFR 70.25(d)).

Prohibited Cosmetic Ingredients	**CFR Citation**
Bithional	21 CFR 700.11
Vinyl chloride	21 CFR 700.14
Certain halogenated salicylanilides	21 CFR 700.15
Zirconium in aerosol products	21 CFR 700.16
Chloroform	21 CFR 700.18
Methylene chloride	21 CFR 700.19
Chlorofluorocarbon propellants	21 CFR 700.23
Prohibited cattle material	21 CFR 700.27

Restricted Cosmetic Ingredients	**CFR Citation**
Mercury compounds	21 CFR 700.13
Hexachlorophene	21 CFR 250.250

Production

You should determine whether written manufacturing and control SOPs have been established (for example, formulations, processing instructions, in-process control methods, packaging instructions, instructions for operating equipment). Procedures should include provisions to ensure that:

- The selection, weighing, and measuring of raw materials and the determination of finished yield are reviewed by a second individual
- Major equipment, transfer lines, containers and tanks used for processing, holding, or filling are identified to indicate contents, batch identification/designation, stage of processing and control status
- There are appropriate measures to prevent contamination with microorganisms, chemicals, filth, or other extraneous material
- There are in-process controls to ensure product uniformity, integrity (for example, in-process batch weights), accurate fill of mixing containers, and adequacy of mixing.
- The theoretical yield for a production batch is compared with the actual yield
- The tamper-resistant packaging and labeling for liquid oral hygiene products and vaginal products meet the requirements of 21 CFR 700.25
- The storage and handling of packaging materials that are intended to come into direct contact with the product prevent selection errors and microbiological or chemical contamination; and
- Finished product packages bear permanent meaningful, unique lot or control numbers and you have a coding system that corresponds to these numbers

Laboratory Controls

You should evaluate laboratory controls including sample collection techniques, specifications, test methods, laboratory equipment, and technician qualifications. Laboratory controls should include provisions to ensure that:

- Raw materials (including water), in-process and finished product samples are tested or examined for identity and compliance with applicable specifications (for example,

physical and chemical properties), microbial contamination, and hazards or other chemical contamination
- Samples are representative of the lot
- Current finished product samples as well as retained product samples are tested for adequacy of preservation against microbial contamination under reasonable conditions of storage and use
- Samples of approved lots of raw materials and finished products are retained for an adequate time period
- Retained samples are stored under conditions which protect their integrity (for example, to avoid contamination and deterioration), and are retested at appropriate intervals to assure continued compliance with established specifications; and
- Returned cosmetics are examined for deterioration, contamination, and compliance with acceptance specifications

Internal Audit

You should determine whether effective procedures for internal audits are followed. At a minimum, internal audit procedures should provide that:
- Internal audits occur regularly or on demand
- Internal audits are conducted by individuals who do not have direct responsibility for the matters being audited
- All observations made during the internal audit are evaluated and shared with appropriate management, production, quality control, and/or lab personnel; and
- Internal audit follow-up confirms the satisfactory completion or implementation of corrective actions

Complaints, Adverse Events, and Recalls

You should review product complaints, consumer adverse event reports, and product recall files and determine the following:
- For complaints:
  Whether there are SOPs for reporting, recording, filing, evaluating, and following up on both written and oral complaints
- For complaints alleging adverse events involving bodily injury:
  - The kind and severity of each reported injury
  - The body part involved
  - Product and code numbers
  - Whether medical treatment was sought, and, if so, the nature of the medical treatment and the name of the attending physician or other healthcare professional
  - Whether resolution of the event occurred, with or without long-term or persistent effects (If long-term or persistent effects occurred, the nature of those effects)

  - The name(s) and location(s) of any poison control center, government agency, physicians group, etc., to whom formula information and/or toxicity data has been provided; and
  - Whether you are voluntarily reporting adverse events to FDA through the MedWatch program
- For voluntary product recalls, the guidelines in 21 CFR part 7, Subpart C, should be considered, including:
  - Whether there is a proposed strategy for conducting a recall
  - Whether recall notifications are capable of being initiated promptly
  - Whether the appropriate FDA district office has been notified of recalls
  - Whether recalled products have been identified and stored separately in a secure area until the firm has made a decision about the proper disposition or correction consistent with the degree of risk of the recalled product; and
  - Whether FDA's guidance as outlined in 21 CFR 7.59 has been considered

Guidance for Industry: Registration and Listing of Cosmetic Product Facilities and Products

Additional copies are available from:
Office of the Chief Scientist
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 1, Room 3317
Silver Spring, MD 20903
(Tel) 301-796-4880
https://www.fda.gov/cosmetics/cosmetics-guidance-regulation/cosmetics-guidance-documents

Appendix B of this guidance that describes frequently asked questions and answers is being distributed for comment purposes only.

Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that FDA considers your comment on the Appendix B before we begin work on the final version of Appendix B, submit either electronic or written comments on this document within 30 days of publication in the Federal Register of the notice announcing the availability of the guidance.

Submit electronic comments to http://www/regulations.gov. Submit written comments on the guidance to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2023-D-1716 as listed in the notice of availability that publishes in the *Federal Register.*

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Chief Scientist

December 2023

Table of Contents

Registration and Listing of Cosmetic Product Facilities and Products: Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. Introduction

This guidance provides recommendations and instructions to assist persons submitting cosmetic product facility registrations and product listings to FDA. This guidance document explains, among other things:

- The statutory requirement to submit cosmetic product facility registrations and product listings;
- Definitions;
- Who is responsible for making the submissions;
- What information to include in the submissions;
- How to make the submissions; and
- When to make the submissions.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. Background

On December 29, 2022, the President signed the Consolidated Appropriations Act, 2023 (Pub. L. 117-328) into law, which included the Modernization of Cosmetics Regulation Act of 2022 (MoCRA). Among other provisions, MoCRA added section 607 to the Federal Food, Drug, and Cosmetic Act (FD&C Act), establishing requirements for cosmetic product facility registration and product listing.

[1] This guidance has been prepared by the Office of Cosmetics and Colors, in the Center for Food Safety and Applied Nutrition, and the Office of the Chief Scientist at the U.S. Food and Drug Administration.

Section 607(a) of the FD&C Act requires every person that owns or operates a facility that "engages in the manufacturing or processing of a cosmetic product for distribution in the United States" to register each facility with FDA.

Section 607(c) of the FD&C Act requires that for each cosmetic product, the responsible person must submit to FDA "a cosmetic product listing."

FDA previously had a voluntary cosmetic registration program (see 21 CFR Parts 710 and 720). FDA ended its voluntary registration program as of March 27, 2023, while we worked toward establishing a new system, including a submission portal for the cosmetic product facility registrations and product listings mandated by MoCRA.[2] Information in the voluntary cosmetic registration program will not be transferred to this new system. Because the information in the voluntary cosmetic registration program differs from the information required to be submitted under MoCRA, FDA does not consider previous submissions to the voluntary cosmetic registration program to satisfy the registration and listing requirements mandated by MoCRA.

FDA has developed an electronic submission portal, Cosmetics Direct, to help streamline submission and receipt of registration and product listing information under section 607 of the FD&C Act. FDA has developed paper forms (FDA Form 5066 and 5067) as an alternative submission tool. As an additional alternative, users may transmit submissions through FDA's Electronic Submissions Gateway (ESG) as described in section III.E. below. FDA strongly encourages electronic submissions to facilitate efficiency and timeliness of data submission and management for the agency. Cosmetics Direct, technical assistance documents and paper submission forms can be accessed at: https://www.fda.gov/cosmetics/registration-listing-cosmetic-product-facilities-and-products.

Certain small businesses, as defined in section 612 of the FD&C Act, are not required to register facilities and list cosmetic product(s) (refer to section III.A. and III.B. below).

Failure to register or submit listing information in accordance with section 607 of the FD&C Act is a prohibited act under section 301(hhh) of the FD&C Act (21 U.S.C. 331(hhh)).

III. Questions and Answers

A. What definitions apply?

We plan to use the following definitions in implementing the registration and product listing requirements of section 607 of the FD&C Act:

[2] For more information, refer to FDA's Constituent Update "FDA Has Stopped Accepting Submissions to the Voluntary Cosmetic Registration Program (VCRP)" at: https://www.fda.gov/food/cfsan-constituent-updates/fda-has-stopped-accepting-submissions-voluntary-cosmetic-registration-program-vcrp.

CONTRACT MANUFACTURER. — means a facility that manufactures or processes a cosmetic product on behalf of another entity.

COSMETIC PRODUCT. — as defined in section 604(2) of the FD&C Act, means a preparation of cosmetic ingredients with a qualitatively and quantitatively set composition for use in a finished product.

DUNS NUMBER. — The Data Universal Numbering System (DUNS) number is a unique nine-digit identification number provided by Dun & Bradstreet (D&B). The DUNS Number is site-specific. Therefore, each distinct physical location of an entity (such as branches, divisions, and headquarters) may be assigned a DUNS number.

FACILITY. — as defined in section 604(3) of the FD&C Act, includes any establishment (including an establishment of an importer) that manufactures or processes cosmetic products distributed in the United States.

This term does not include any of the following:

(i) Beauty shops and salons, unless such establishment manufactures or processes cosmetic products at that location;

(ii) Cosmetic product retailers, including individual sales representatives, direct sellers (as defined in section 3508(b)(2) of the Internal Revenue Code of 1986), retail distribution facilities, and pharmacies, unless such establishment manufactures or processes cosmetic products that are not sold directly to consumers at that location;

(iii) Hospitals, physicians' offices, and health care clinics;

(iv) Public health agencies and other nonprofit entities that provide cosmetic products directly to the consumer;

(v) Entities (such as hotels and airlines) that provide complimentary cosmetic products to customers incidental to other services;

(vi) Trade shows and other venues where cosmetic product samples are provided free of charge;

(vii) An establishment that manufactures or processes cosmetic products that are solely for use in research or evaluation, including for production testing and not offered for retail sale;

(viii) An establishment that solely performs one or more of the following with respect to cosmetic products:

- Labeling,
- Relabeling,
- Packaging,
- Repackaging,
- Holding,
- Distributing.

For purposes of determining whether an establishment solely performs one or more of the activities listed under (viii), the terms 'packaging' and 'repackaging' do not include filling a product container with a cosmetic product.

FEI. — is an acronym which stands for FDA Establishment Identifier. It is also known as the Firm or Facility Establishment Identifier. The FEI number is a unique identifier assigned by the FDA to identify firms associated with FDA-regulated products. FDA intends to use a facility's FEI number as the cosmetic product facility's registration number.

MANUFACTURING OR PROCESSING OF A COSMETIC PRODUCT. — means engaging in one or more steps in the making of any cosmetic product by chemical, physical, biological, or other procedures, including manipulation, sampling, testing, or control procedures applied to the product.

OPERATOR. — means a person, as defined in section 201(e) of the FD&C Act (21 U.S.C 321(e)), who has management authority over an establishment.

OWNER. — means a person, as defined in section 201(e) of the FD&C Act (21 U.S.C. 321(e)), who has an ownership interest in an establishment.

RESPONSIBLE PERSON. — as defined in section 604(4) of the FD&C Act, means the manufacturer, packer, or distributor of a cosmetic product whose name appears on the label of such cosmetic product in accordance with section 609(a) of the FD&C Act or section 4(a) of the Fair Packaging and Labeling Act.

SMALL BUSINESSES. — as defined in section 612 of the FD&C Act, means responsible persons, and owners and operators of facilities, whose average gross annual sales in the U.S. of cosmetic products for the previous 3-year period is less than $1,000,000, adjusted for inflation,[3] and who do not engage in the manufacturing or processing of certain cosmetic products described in section 612(b) of the FD&C Act. A small business is exempt from the registration and listing requirements.

> Under section 612(b) of the FD&C Act, regardless of their average gross annual sales, businesses that engage in the manufacturing or processing of the following are not exempt from the registration and listing requirements:
>
> - Cosmetic products that regularly come into contact with mucus membrane of the eye under conditions of use that are customary or usual;
> - Cosmetic products that are injected;
> - Cosmetic products that are intended for internal use; or

[3] We recommend using the Implicit Price Deflator for GDP, updated annually by the Bureau of Economic Analysis, when adjusting for inflation. Please refer to: https://apps.bea.gov/iTable/?reqid=19&step=3&isuri=1&1921=survey&1903=13.

- Cosmetic products that are intended to alter appearance for more than 24 hours under conditions of use that are customary or usual and removal by the consumer is not part of such conditions of use that are customary or usual.

B. Who registers a facility and submits product listing information under section 607 of the FD&C Act?

1. Registration of a Facility

Section 607(a)(1) of the FD&C Act requires every person that owns or operates a facility that engages in the manufacturing or processing of a cosmetic product for distribution in the United States to register each facility, except in the following instances:

- A facility that is exempt from registration as a "small business" as described section III.A. above;
- A facility that is also subject to the requirements in chapter V of the FD&C Act (for drugs and devices) unless the facility also manufactures or processes cosmetic products that are not subject to the requirements of chapter V of the FD&C Act (see section 613 of the FD&C Act).

As provided under section 607(a)(3) of the FD&C Act, if a facility manufactures or processes cosmetic products on behalf of a responsible person (i.e., a contract manufacturer), only a single registration is required for such facility even if the facility is manufacturing or processing its own cosmetic products or cosmetic products on behalf of more than one responsible person. A responsible person whose products are manufactured or processed at such facility may submit the facility registration for such facility. Under this approach, an owner or operator of a contract manufacturing facility would not register such facility if the responsible person submitted the facility registration.

2. Product Listing

Section 607(c) of the FD&C Act requires that for each cosmetic product, the responsible person must submit a cosmetic product listing, or ensure such submission is made, except in the following instances:

- The responsible person that is exempt as a "small business" as described in section III.A. above;
- The cosmetic product that is also subject to the requirements in chapter V of the FD&C Act (for drugs and devices). For example, if the product is both a drug and a cosmetic product under the FD&C Act, a cosmetic product listing is not required to be submitted for such product (see section 613 of the FD&C Act), but the listed product should be identified as both a drug and a cosmetic in the drug listing submission.

C. What information is submitted as part of facility registration and product listing under section 607 of the FD&C Act?

1. Registration

Under sections 607(a) and 607(b)(2) of the FD&C Act, the following information must be submitted in a facility registration:

- the name of the owner and/or operator of the facility;
- the facility's name, physical address, email address, and telephone number;
- with respect to any foreign facility, the contact for the United States agent[4] of the facility (name and phone number), and, if available, the electronic contact information (email);
- the facility registration number, if any, previously assigned by FDA;[5]
- all brand names under which cosmetic products manufactured or processed in the facility are sold;
- the product category or categories (refer to Appendix A below) and responsible person for each cosmetic product manufactured or processed at the facility; and
- type of submission (initial, amended, biennial renewal, or abbreviated renewal, for further information see discussion in section III.F.1).

Obtaining the assigned facility registration number is the first step *before* starting the registration submission.

FDA also requests that the following additional optional information be submitted:

---

[4] With respect to a foreign facility, a United States agent ("U.S. agent") is required for registration purposes. The U.S. agent is the person, which includes an individual or business entity, that resides in the U.S. or maintains a U.S. place of business and is physically present in the U.S. A U.S. agent should not be a mailbox, answering machine or service, or other place where an individual acting as the foreign facility's agent is not physically present.

[5] The facility registration number is the FDA Establishment Identifier (FEI). To facilitate the registration process, the owner or operator of a facility will need to obtain an FEI number before submitting the facility registration. Request for issuance of FEI numbers associated with registration for cosmetic product facilities are typically processed in 7-10 business days. A facility that was previously assigned an FEI number in connection with other business with FDA should use the same FEI number and should not request a new FEI. For more information, including how to determine if an entity already has an FEI number, refer to the webpage at: https://www.accessdata.fda.gov/scripts/feiportal/index.cfm?action=portal.login. If your entity does not have an FEI number assigned by FDA, send a request to feiportal@fda.hhs.gov and provide the following information:

- Legal firm name
- Any alternate firm names, including those used for "doing business as" purposes
- Physical address
- Designated mailing address
- Name and contact information of the designated contact person
- A comprehensive list of activities conducted at this specific location (e.g., drug manufacturing, food packaging, etc.)
- Any registration numbers associated with other FDA Center(s), if applicable
- Any former names the firm was known by
- Any previous addresses linked to the firm

- parent company name (if applicable);
- facility DUNS Number; and
- additional contact information for individuals associated with the registration.

In addition, FDA requests that individuals submitting registration and listing information to attest to the accuracy and veracity of the information submitted.

2. Product Listing

Under section 607(c) of the FD&C Act, the following information must be submitted in a cosmetic product listing:

- the facility registration number of each facility where the cosmetic product is manufactured or processed;[6]
- the name and contact number of the responsible person and the name for the cosmetic product, as such name appears on the label;
- the applicable cosmetic category or categories for the cosmetic product (refer to Appendix A below);
- a list of ingredients in the cosmetic product, including any fragrances, flavors, or colors, with each ingredient identified by the name, as required under section 701.3 of title 21, Code of Federal Regulations (or any successor regulations), or by the common or usual name of the ingredient;
- the product listing number, if any previously assigned; and
- type of submission (initial, update to content (annual), abbreviated renewal).

Under section 607(c)(4)(B), a single listing submission for a cosmetic product may include multiple cosmetic products with identical formulations, or formulations that differ only with respect to colors, fragrances or flavors, or quantity of contents.

FDA also requests that the following additional optional information be submitted:

- parent company name (if applicable);
- type of business (as listed on the label), i.e., manufacturer, packer, or distributor;
- image of the label (currently jpg files are accepted);
- product webpage link;
- whether the cosmetic product is for professional use only;
- responsible person DUNS Number for address listed on product label;
- Unique Ingredient Identifiers (UNIIs)[7]; and

[6] The responsible person will need to obtain the relevant facility registration number(s) for each facility where its cosmetic products are manufactured or processed, because the facility registration number(s) is required for the product listing submission. If the facility is exempt from registration, for example because it is a small business, and has no facility registration number, then facility name/address can be provided instead.

[7] For more information and to search for UNIIs please refer to the webpage at: https://precision.fda.gov/uniisearch. For UNII requests contact: FDA-SRS@fda.hhs.gov.

- additional contact information for individuals associated with the listing.

In addition, FDA requests that individuals submitting registration and listing information attest to the accuracy and veracity of the information submitted.

D. Is cosmetic product facility registration and cosmetic product listing information submitted under section 607 of the FD&C Act available for public disclosure?

The product listing number will not be available for public disclosure (section 607(d) of the FD&C Act). Further, under section 607(e) of the FD&C Act, FDA will not disclose information from a facility registration on the brand names under which cosmetic products manufactured or processed in the facility are sold, or from a product listing on the facility registration number of the facility where the cosmetic product is manufactured or processed, in response to a request under the Freedom of Information Act (FOIA) (5 U.S.C. 552). All other information from cosmetic product facility registration and listing would be available for public disclosure consistent with the FOIA, FDA's disclosure regulations under 21 CFR Part 20, and other applicable federal law. FDA intends to make relevant information from cosmetic product facility registration and listing available to the public to the extent permitted by law.

E. How do you submit registration and product listing information required under section 607 of the FD&C Act?

Cosmetics Direct is an electronic submission portal designed to help streamline submission and receipt of registration and product listing information required by section 607 of the FD&C Act. While electronic submission is not required, FDA strongly encourages electronic submissions to facilitate efficiency and timeliness of data submission and management for the agency. Registration and listing data are submitted electronically using structured product labeling (SPL)[8] format. Future updates to industry submissions are intended to be efficient to submit because information from a previous submission can be applied without re-entering all information. Technical assistance will be available for users by contacting a help desk for Cosmetics Direct.

As an alternative, users may transmit SPL-formatted submissions through FDA's Electronic Submissions Gateway (ESG),[9] or any SPL authoring software including Xforms.[10] The FDA ESG system requires users to apply for a free account before submitting data, a process which can take one to three weeks. FDA therefore urges those who are planning to use the ESG to

[8] The Structured Product Labeling (SPL) is a document markup standard approved by Health Level Seven (HL7) and adopted by FDA as a mechanism for exchanging product and facility information.
[9] For more information on FDA's Electronic Submissions Gateway, please refer to the webpage at https://www.fda.gov/industry/electronic-submissions-gateway
[10] For more information on Xforms, please refer to the webpage at https://www.fda.gov/industry/structured-product-labeling-resources/spl-xforms In addition, the technical details on using SPL for registration and listing are available in the FDA's SPL Implementation Guide available at https://www.fda.gov/media/84201/download.

apply for ESG accounts well in advance of the deadline for data submission. Technical assistance is available for users by contacting the ESG at ESGHelpDesk@fda.hhs.gov

FDA developed paper forms (FDA Form 5066 and 5067) as another alternative submission tool. Both the Cosmetics Direct and the paper forms are accessible at https://www.fda.gov/cosmetics/registration-listing-cosmetic-product-facilities-and-products.

F. When must you register and list under section 607 of the FD&C Act?

1. Registration

a. Initial Registration

Every person that, on December 29, 2022, owns or operates a facility that engages in the manufacturing or processing of a cosmetic product for distribution in the United States must register each facility no later than December 29, 2023 (section 607(a)(1)(A) of the FD&C Act).

Every person that owns or operates a facility that first engages, after December 29, 2022, in manufacturing or processing of a cosmetic product for distribution in the United States, must register such facility within 60 days of first engaging in such activity or by February 27, 2024, whichever is later (section 607(a)(1)(B) of the FD&C Act).

Note: On November 8, 2023, FDA issued a guidance for industry titled "Compliance Policy for Cosmetic Product Facility Registration and Cosmetic Product Listing." This guidance explains that FDA does not intend to enforce the requirements under section 607 of the FD&C Act related to cosmetic product facility registration until **July 1, 2024**.

b. Amended Registration

Every person who is required to register must update their registration within 60 days of any changes to the information required for registration (section 607(a)(4) of the FD&C Act) (an "amended" registration). This includes any changes that result in cancellation of the registration.

c. Renewal of Registration

Every person who is required to register a facility must renew such registration biennially (i.e., every two years) (section 607(a)(2) of the FD&C Act).

FDA is providing for an abbreviated renewal of registrations when there have not been any updates to the registration since the most recent facility registration submission, as required under section 607(a)(4) of the FD&C Act.

Note: In the case of a contract manufacturer, a facility registration may be submitted by the contract manufacturer or any responsible person whose products are manufactured or processed at such facility (section 607(a)(3) of the FD&C Act). Also, note that the renewal period and timeframe to submit updates for a cosmetics product facility registration may be different than for other FDA-regulated products for which the facility may also be required to register.

2. Product Listing

a. Initial Listing

The responsible person of a cosmetic product that is marketed on December 29, 2022, must submit a cosmetic product listing, or ensure such submission is made, not later than December 29, 2023, or for a cosmetic product that is first marketed after December 29, 2022, within 120 days of marketing such product in interstate commerce (section 607(c)(2) of the FD&C Act). Consistent with the approach for registration of a facility that starts manufacturing or processing cosmetic products after December 29, 2022 (section 607(a)(1)(B) of the FD&C Act), FDA expects the product listing for a cosmetic product first marketed after December 29, 2022, to be submitted within 120 days of marketing the product, or within 120 days of December 29, 2023 (which is April 27, 2024), whichever is later.

Note: On November 8, 2023, FDA issued a guidance for industry titled "Compliance Policy for Cosmetic Product Facility Registration and Cosmetic Product Listing." This guidance explains that FDA does not intend to enforce the requirements under section 607 of the FD&C Act related to cosmetic product listing until **July 1, 2024**.

b. Update to Content and Renewal

The responsible person must provide any updates to such listing annually (section 607(c)(5) of the FD&C Act). This includes an update that the product was discontinued.

FDA is providing for an abbreviated process for the renewal of any cosmetic product listing, as required under section 607(c)(3), for which there has been no change since the responsible person submitted the previous listing.

G. What if my product is both a drug and a cosmetic product? Do have I have to comply with cosmetic product facility registration and cosmetic product listing requirements under section 607 of the FD&C Act?

A cosmetic product that is also a drug is not subject to the listing requirements under section 607 of the FD&C Act. Likewise, a facility that manufactures or processes cosmetic products that are also drugs is not subject to the registration requirement under section 607 unless it also manufactures or processes cosmetic products that are not also drugs (see section 613 of the FD&C Act). Cosmetic product facility registration and product listing are available using the same electronic submission process available to register an establishment and list a drug with FDA. This will help to streamline the process of submitting registration and listing information for cosmetics facilities and products for entities that also submit drug establishment and listing information.

H. Does FDA charge a fee to submit a registration or product listing under section 607 of the FD&C Act?

No. There is no fee to submit a registration or product listing to FDA under section 607 of the FD&C Act.

APPENDIX A

Cosmetic Product Categories and Codes

(01) ***Baby products.***
(a) Baby shampoos.
(b) Lotions, oils, powders, and creams.
(c) Baby wipes.
(d) Other baby products.
1. Leave-on.
2. Rinse-off.

(02) ***Bath preparations.***
(a) Bath oils, tablets, and salts.
(b) Bubble baths.
(c) Bath capsules.
(d) Other bath preparations.

(03) ***Eye makeup preparations (other than children's eye makeup preparations).***
(a) Eyebrow pencils.
(b) Eyeliners.
(c) Eye shadows.
(d) Eye lotions.
(e) Eye makeup removers.
(f) False eyelashes.
(g) Mascaras.
(h) Eyelash and eyebrow adhesives, glues, and sealants.
(i) Eyelash and eyebrow preparations (primers, conditioners, serums, fortifiers).
(j) Eyelash cleansers.
(k) Other eye makeup preparations.

(04) ***Children's eye makeup preparations.***
(a) Children's eyeshadows.
(b) Other children's eye makeup.

(05) ***Fragrance preparations.***
(a) Colognes and toilet waters.
(b) Perfumes.
(c) Powders (dusting and talcum) (excluding aftershave talc).
(d) Other fragrance preparations.

(06) ***Hair preparations (non-coloring).***
(a) Hair conditioners.
1. Leave-on.
2. Rinse-off.

(b) Hair sprays (aerosol fixatives).
(c) Hair straighteners.
(d) Permanent waves.
(e) Rinses (non-coloring).
(f) Shampoos (non-coloring).

1. Leave-on.
2. Rinse-off.

(g) Tonics, dressings, and other hair grooming aids.
(h) Wave sets.
(i) Other hair preparations.
1. Leave-on.
2. Rinse-off.

(07) ***Hair coloring preparations.***
(a) Hair dyes and colors (all types requiring caution statement and patch test).
(b) Hair tints.
(c) Hair rinses (coloring).
1. Leave-on.
2. Rinse-off.

(d) Hair shampoos (coloring).
1. Leave-on.
2. Rinse-off.

(e) Hair color sprays (aerosol).
(f) Hair lighteners with color.
(g) Hair bleaches.
(h) Eyelash and eyebrow dyes.
(i) Other hair coloring preparations.
1. Leave-on.
2. Rinse-off.

(08) ***Makeup preparations (not eye)(other than makeup preparations for children).***
(a) Blushers and rouges (all types).
(b) Face powders.
(c) Foundations.
1. Traditional applications.
2. Airbrush applications.

(d) Leg and body paints.
1. Traditional applications.
2. Airbrush applications.

(e) Lipsticks and lip glosses.
(f) Makeup bases.
1. Traditional applications.
2. Airbrush applications.

(g) Makeup fixatives.
(h) Other makeup preparations.
1. Traditional applications.
2. Airbrush applications.

(09) ***Makeup preparations for children (not eye).***
(a) Children’s blushers and rouges (all types).
(b) Children’s face paints.
(c) Children’s face powders.
(d) Children’s foundations.
(e) Children’s lipsticks and lip glosses.

(f) Children's color hairsprays.
(g) Other children's makeup.
(10) ***Manicuring preparations.***
(a) Basecoats and undercoats.
(b) Cuticle softeners.
(c) Nail creams and lotions.
(d) Nail extenders.
(e) Nail polishes and enamels.
(f) Nail polish and enamel removers.
(g) Other manicuring preparations.
(11) ***Oral products.***
(a) Dentifrices (aerosols, liquids, pastes, and powders).
(b) Mouthwashes and breath fresheners (liquids and sprays).
(c) Other oral products.
(12) ***Personal cleanliness.***
(a) Bath soaps and body washes.
(b) Deodorants (underarm).
    1. Sticks, roll-ons, gels, creams, and wipes.
    2. Sprays.
(c) Douches.
(d) Feminine deodorants.
    1. Leave-on.
    2. Rinse-off.
(e) Disposable wipes.
(f) Other personal cleanliness products.
    1. Leave-on.
    2. Rinse-off.
(13) ***Shaving preparations.***
(a) Aftershave lotions.
(b) Beard softeners.
(c) Men's talcum.
(d) Pre-shave lotions (all types).
(e) Shaving creams (aerosol, brushless, and lather).
(f) Shaving soaps (cakes, sticks, etc.).
(g) Other shaving preparation products.
(14) ***Skin care preparations, (creams, lotions, powder, and sprays).***
(a) Cleansing (cold creams, cleansing lotions, liquids, and pads).
(b) Depilatories.
(c) Face and neck (excluding shaving preparations).
    1. Leave-on.
    2. Rinse-off.
(d) Body and hand (excluding shaving preparations).
    1. Leave-on.
    2. Rinse-off.
(e) Foot powders and sprays.
(f) Moisturizing.

(g) Night.
(h) Paste masks (mud packs).
(i) Skin fresheners.
(j) Other skin care preparations.
1. Leave-on.
2. Rinse-off.

(15) ***Suntan preparations.***
(a) Suntan gels, creams, and liquids.
(b) Indoor tanning preparations.
1. Traditional applications (creams, lotions, etc.).
2. Airbrush applications.
3. Spray applications.
4. Professional airbrush tanning applications.
5. Professional spray tanning applications.

(c) Other suntan preparations.
(16) ***Tattoo preparations.***
(a) Permanent tattoo inks.
(b) Temporary tattoo inks.
(c) Other tattoo preparations.
(17) ***Other preparations*** *(i.e., those preparations that do not fit another category)***.**

APPENDIX B[11]

Frequently Asked Questions and Answers

Q1. Do owners and operators of facilities that only manufacture or process cosmetic ingredients need to register their facilities? Does a responsible person need to submit a product listing for cosmetic ingredients?

A. No, at this time, FDA only expects non-exempt facilities to register if they manufacture or process the final formulation of cosmetic ingredients (including a final formulation that includes a single ingredient). This includes final formulations that have not yet been packaged. FDA only expects non-exempt responsible persons to list cosmetic products that are marketed for users (e.g., consumers or professional use).

Q2. Can a consultant be a "responsible person" under section 607 of the FD&C Act?

A. A consultant can only be a responsible person if they meet the definition of "responsible person" in section 604(4) of the FD&C Act. A "responsible person" as defined in section 604(4) of the FD&C Act, means the manufacturer, packer, or distributor of a cosmetic product whose name appears on the label of such cosmetic product in accordance with section 609(a) of the FD&C Act or section 4(a) of the Fair Packaging and Labeling Act.

Q3. Can a company located outside of the U.S. be the "responsible person"?

A. "Responsible person," as defined in section 604(4) of the FD&C Act, means the manufacturer, packer, or distributor of a cosmetic product whose name appears on the label of such cosmetic product in accordance with section 609(a) of the FD&C Act or section 4(a) of the Fair Packaging and Labeling Act. A company located outside of the U.S. could be a "responsible person" so long as they are the manufacturer, packer, or distributor of the cosmetic product. However, we note that, under section 609(a) of the FD&C Act, each cosmetic product shall bear a label that includes a domestic address, domestic phone number, or electronic contact information, which may be a website, through which the responsible person can receive adverse event reports with respect to such cosmetic product. We recommend that firms consider when selecting electronic contact information, such as an email address or a website (whether foreign or domestic), how they can best respond to these reports and meet maintenance, inspection, and reporting requirements under section 605 of the FD&C Act.

Q4. Is the brand name the same as the product name?

A. No. FDA does not consider the brand name and product name to be the same.

[11] This section of the guidance, Appendix B (designated with a shaded background), is being distributed for comment purposes only.

The product name is generally considered the statement of identity, as required under 21 CFR 701.11. The statement of identity provides information about the type or kind of cosmetic product in the package to help the consumer understand the functional use of the product.

The brand name is the distinguishing name used by a company to identify a commercial product on the product label. The brand name may be proprietary and/or registered as a trademark.

Q5. What are examples of products whose manufacture does not qualify the responsible person or facility for the small business exemptions under section 612 of the FD&C Act?

A. Section 612 of the FD&C Act provides exemptions to certain small businesses from the requirements of sections 606 (Good Manufacturing Practice) and 607 (Registration and Product Listing). However, such exemptions from the requirements of sections 606 and 607 of the FD&C Act do not apply to any responsible person or facility engaged in the manufacturing or processing of any of the following products listed in section 612(b) of the FD&C Act:

(1) Cosmetic products that regularly come into contact with mucus membrane of the eye under conditions of use that are customary or usual.

(2) Cosmetic products that are injected.

(3) Cosmetic products that are intended for internal use.

(4) Cosmetic products that are intended to alter appearance for more than 24 hours under conditions of use that are customary or usual and removal by the consumer is not part of such conditions of use that are customary or usual.

Q6. What are examples of products that regularly come into contact with the mucus membrane of the eye?

A. While there may be certain exceptions, an eye makeup remover, a liquid or mucosal eyeliner, or a false eyelash adhesive may regularly come into contact with the mucous membrane of the eye under conditions of use that are customary or usual, such that they would not qualify the small business exemption (see section 612(b)(1) of the FD&C Act). However, facial cleaners, moisturizers, and serums generally would not be expected to regularly come into contact with the mucous membrane of the eye under conditions of use that are customary or usual.

Q7. What are examples of products that are intended to alter appearance for more than 24 hours?

A. Examples of cosmetic products that are intended to alter the appearance for more than 24 hours and removal by the consumer is not part of such conditions of use that are customary or usual, as described in section 612(b)(4) of the FD&C Act, may include certain nail polishes, some hair products, some eyebrow dyes, and certain leave-on skin preparations. To

determine if a product falls under section 612(b)(4) of the FD&C Act one should consider product labeling, including directions for use, as well as the uses of the product that are not indicated in the labeling but are customary or usual.

Q8. If a facility engages in the manufacturing or processing of cosmetic products listed in section 612(b) of the FD&C Act, does the facility need to include information required under section 607(b)(2)(D) and (E) for only the cosmetic products listed in section 612(b), or for all of the cosmetic products manufactured or processed by the facility?

A. The exemptions in section 612 of the FD&C Act apply to responsible persons and owners and operators of facilities that meet the definition of a small business in section 612(a). Thus, a facility is required to include information required under section 607(b)(2)(D) and (E) for all of the cosmetic products manufactured or processed by the facility if a facility manufactures or processes any of the following cosmetic products:

(1) Cosmetic products that regularly come into contact with mucus membrane of the eye under conditions of use that are customary or usual.

(2) Cosmetic products that are injected.

(3) Cosmetic products that are intended for internal use.

(4) Cosmetic products that are intended to alter appearance for more than 24 hours under conditions of use that are customary or usual and removal by the consumer is not part of such conditions of use that are customary or usual.

Q9. Where can I submit documentation that my business meets the small business exemption in order to receive an exemption certificate from FDA?

A. FDA is not generally asking companies to submit this information nor does FDA provide small business exemption certificates for cosmetic product facilities or responsible persons.

Q10. Does an importer need to register and/or list under 607 of the FD&C Act?

A. If an importer meets the definition of a facility and/or a responsible person in section 604 of the FD&C Act, and does not meet any exemption, then they must comply with any applicable registration or listing requirements. Otherwise, the importer is not required to register or list.

Q11. Does a laboratory that only performs testing on cosmetic products used for research and development need to register?

A. No. If a laboratory tests cosmetic products that are solely for use in research, development, or evaluation, and that are not offered for retail sale, it does not need to register because it is an

establishment that is not included in the definition of facility in section III.B. above (see section 604(3)(B)(vii) of the FD&C Act).

Q12. Does a laboratory that performs cosmetic product batch release testing need to register?

A. Yes. Cosmetic product batch release testing is part of manufacturing and processing. Laboratories conducting this testing are considered facilities subject to the registration requirements.

Q13. My company owns 2 buildings with 2 addresses, and 1 of the buildings is for storage only. Do we need to register the building used only for storage?

A. No. An establishment that solely performs storage (holding) with respect to cosmetic products is not required to register under section 607 of the FD&C Act.

Q14. If a contract manufacturer of cosmetic products is located outside of the United States are they required to be registered with the FDA under section 607 of the FD&C Act? Is there an exemption from registration if the contract manufacturer follows ISO22716?

A. If a contract manufacturer manufactures or processes cosmetic product(s) distributed in the United States, then the contract manufacturing facility must be registered with the FDA, even if the contract manufacturer is located outside of the United States. More information, including on exemptions, are described in section III above. There is not an exemption from registration for following ISO22716.

Q15. Do hair coloring preparations (including hair dyes) need to be listed?

A. Yes. Hair coloring preparations, including hair dyes, are cosmetic products and therefore need to be listed, unless an exemption applies.

Q16. Do hairbrushes and wigs need to be listed?

A. No. We do not expect hairbrushes and wigs to be listed.

Q17. My cosmetic products don't fit into any of the product categories provided in Appendix A. Therefore, what product category and code should be used?

A. We recommend that you select the product category and code in Appendix A (above) that match most closely and use the "other" category and code if another category and code does not appear to fit. Keep in mind that products intended for use in the eye area should be entered into an eye area product category.

FDA intends to periodically update the product categories and codes. Any proposed update to the product categories and codes FDA intends to publish as draft guidance on our website, with a notice in the Federal Register announcing that the draft guidance document is

available. After providing an opportunity for public comment on the draft guidance, FDA will:

(A) Review any comments received and prepare the final version of the guidance document that incorporates suggested changes, when appropriate;

(B) Publish a notice in the Federal Register announcing that the guidance document is available;

(C) Post the guidance document on the Internet and make it available in hard copy; and

(D) Implement the guidance document.

Q18. What is the receipt date for registrations and listings submitted via paper form?

A. When FDA receives a paper submission, the submission is assigned a receipt date. The receipt date for a paper submission is the date on which the submission is deemed to have arrived at FDA. A paper submission is deemed to have arrived at FDA on the date on which it arrived physically at the appropriate receiving unit, while open for business, for the FDA unit that will review the submission. If paper registration and listing forms are mailed, we recommend using a method that includes tracking.

FDA encourages electronic submission of registration and listing for cosmetic product facilities and products.

Q19. The cosmetic establishment registration is to be renewed biennially. Does this mean the biennial renewal has to be done every two years from the date of initial registration?

A. Yes, a cosmetic product facility needs to renew its registration every two years from the date of initial registration.

Compliance Policy for Cosmetic Product Facility Registration and Cosmetic Product Listing

Guidance for Industry

Additional copies are available from:

Office of the Chief Scientist
U.S. Food and Drug Administration
10903 New Hampshire Ave, Bldg. 1, Room 3317
Silver Spring, MD 20903
Phone Number: 301-796-4880
Email address: QuestionsAboutMoCRA@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Chief Scientist (OCS)

November 2023

TABLE OF CONTENTS

Compliance Policy for Cosmetic Product Facility Registration and Cosmetic Product Listing Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist owners or operators of cosmetic product facilities that are subject to the requirements related to facility registration and responsible persons that are subject to the requirements related to cosmetic product listing under the Federal Food, Drug, and Cosmetic Act (FD&C Act). This guidance document discusses FDA's compliance policy for these requirements. FDA intends to delay enforcement of these requirements for six months to help ensure that industry has sufficient time to submit facility registration and product listing information.

This guidance is being implemented without prior public comment because the Agency has determined that prior public participation is not feasible or appropriate. 21 CFR 10.115(g)(2). This guidance is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices. 21 CFR 10.115(g)(5).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

On December 29, 2022, the President signed the Consolidated Appropriations Act, 2023 (Pub. L. 117-328) into law, which included the Modernization of Cosmetics Regulation Act of 2022 (MoCRA). Among other provisions, MoCRA added section 607 to the FD&C Act (21 U.S.C. 364c), establishing requirements for cosmetic product facility registration and cosmetic product listing.

[1] This guidance has been prepared by the Office of the Chief Scientist (OCS) in cooperation with the Office of Cosmetics and Colors (OCAC)/Center for Food Safety and Applied Nutrition (CFSAN) at the Food and Drug Administration.

Section 607(a) of the FD&C Act requires every person that owns or operates a facility[2] that "engages in the manufacturing or processing of a cosmetic product for distribution in the United States" to register each facility with FDA. Section 607(a)(1)(A) provides that owners or operators of facilities engaged in the manufacturing or processing of a cosmetic product on December 29, 2022, must register each facility no later than December 29, 2023. Owners or operators of facilities that first engage in manufacturing or processing a cosmetic product after December 29, 2022, must register such facilities within 60 days of first engaging in such activity or by February 27, 2024, whichever is later (Section 607(a)(1)(B)).

Section 607(c) of the FD&C Act requires that for each cosmetic product, the responsible person[3] must submit to FDA "a cosmetic product listing" or ensure that such submission is made. Section 607(c)(2) of the FD&C Act provides that the responsible person for a cosmetic product that was marketed on December 29, 2022, must submit a cosmetic product listing, no later than December 29, 2023, or for a cosmetic product that is first marketed after December 29, 2022, within 120 days of distributing such product in interstate commerce.

Certain small businesses, as defined in section 612 of the FD&C Act (21 U.S.C. 364h), are not required to register facilities and list cosmetic product(s). In addition, a facility is not required to register if it is also subject to the requirements in chapter V of the FD&C Act (for drugs and devices) unless the facility also manufactures or processes cosmetic products that are not subject to the requirements of chapter V of the FD&C Act (see section 613 of the FD&C Act (21 U.S.C. 364i)). A cosmetic product does not need to be listed if it is also subject to the requirements in chapter V of the FD&C Act (for drugs and devices).

FDA issued a draft guidance entitled "Registration and Listing of Cosmetic Product Facilities and Products" on August 8, 2023 (88 FR 53490). The draft guidance, when finalized, will provide recommendations and instructions to assist persons submitting cosmetic product facility registrations and product listings to FDA.

FDA is also developing an electronic submission portal, Cosmetics Direct, to streamline submission and receipt of facility registration and product listing information under section 607 of the FD&C Act, and is developing paper forms (FDA Form 5066 and 5067) as an alternative submission tool. FDA will conduct a pilot program to ensure that the new electronic submission portal is functional and usable so that industry will be able to meet its statutory obligations. As another alternative, users may transmit SPL-formatted submissions through FDA's Electronic Submissions Gateway (ESG),[4] or any SPL authoring software including Xforms.[5] FDA strongly encourages electronic submissions to facilitate efficiency and timeliness of data submission and management for the agency. FDA anticipates that electronic submission, technical assistance documents, and paper submission forms will be available in early December 2023.

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[2] The term "facility" is defined in section 604(3) of the FD&C Act (21 U.S.C. 364(3)).
[3] The term "responsible person" is defined in section 604(4) of the FD&C Act (21 U.S.C. 364(4)).
[4] For more information on FDA's Electronic Submissions Gateway, please refer to the webpage at https://www.fda.gov/industry/electronic-submissions-gateway.
[5] For more information on Xforms, please refer to the webpage at https://www.fda.gov/industry/structured-product-labeling-resources/spl-xforms. In addition, the technical details on using SPL for cosmetic product facility registration and product listing will be available in the FDA's SPL Implementation Guide with Validation Procedures available at https://www.fda.gov/media/84201/download.

III. DISCUSSION

FDA will be ready to accept registration and listing information by the statutory deadline of December 29, 2023, and we encourage companies to meet that deadline if they are able to do so. However, FDA does not intend to enforce the requirements under section 607 of the FD&C Act related to cosmetic product facility registration and cosmetic product listing for an additional six months after the December 29, 2023, statutory deadline, or until **July 1, 2024,** to provide regulated industry additional time to comply with these requirements. In addition, FDA does not intend to enforce the registration requirement for owners or operators of facilities that first engaged in manufacturing or processing a cosmetic product after December 29, 2022, or the listing requirement for cosmetic products first marketed after December 29, 2022, until **July 1, 2024**.

FDA intends to delay enforcement of the cosmetic product facility registration and product listing requirements. Industry has expressed concerns that they need additional time, for example to gather the relevant information required for facility registration and product listing, including obtaining facility registration numbers to associate with cosmetic product listings, obtain access to the electronic submissions database, and enter and submit accurate registration and listing information.

Conducting Remote Regulatory Assessments

Questions and Answers

Draft Guidance for Industry

This draft guidance document is for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2022-D-0810.

For questions or information regarding this guidance, contact the Office of Regulatory Affairs (ORA), Office of Policy, Compliance, and Enforcement (OPCE), Food and Drug Administration at ORAPolicyStaffs@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Regulatory Affairs
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Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Devices and Radiological Health
Center for Food Safety and Applied Nutrition
Center for Tobacco Products
Center for Veterinary Medicine

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Conducting Remote Regulatory Assessments

Questions and Answers

Draft Guidance for Industry

This draft guidance document is for comment purposes only.

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Table of Contents

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Guidance for Industry[1]

This draft guidance, when finalized, represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

In response to the Coronavirus Disease 2019 (COVID-19) pandemic, FDA adapted its operations for field activities to provide oversight of regulated industry while mitigating the spread of COVID-19. One set of tools used during the COVID-19 public health emergency for oversight of FDA-regulated products was remote regulatory assessments (RRAs). The term "RRA" (as defined in the Question and Answers section) is used to describe a category of activities for which FDA may use different terminologies, but that are all considered to be *types* of RRAs, including "remote interactive evaluations"[2] and "remote record reviews." Such activities, along with others identified in this draft guidance, are considered RRAs for purposes of this guidance. In the presence of travel restrictions during the COVID-19 pandemic, FDA utilized RRAs to assess establishments and their compliance with applicable FDA requirements. Based on

[1] This draft guidance has been prepared by the Office of Regulatory Affairs in cooperation with the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, the Center for Food Safety and Applied Nutrition, the Center for Tobacco Products, the Center for Devices and Radiological Health, the Center for Veterinary Medicine, the Office of Food Policy and Response, and the Office of Combination Products.

[2] See Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities, Draft Guidance for Industry, issued October 2023. See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/remote-interactive-evaluations-drug-manufacturing-and-bioresearch-monitoring-facilities. We update guidance documents periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

this experience,[3] FDA has noted the value of RRAs and concluded that they should be used for certain scenarios outside the COVID-19 pandemic and for all types of FDA-regulated products.[4] FDA has developed this guidance to provide answers to frequently asked questions related to RRAs. When finalized, this guidance is intended to help enhance industry's understanding of RRAs, thereby facilitating FDA's process for conducting RRAs.

Throughout this guidance, the terms, "FDA," "the Agency," "we," "us," and "our" refer to the Food and Drug Administration. In this guidance, the term "establishment" includes any facility, entity, person, importer, or site, whether foreign or domestic, subject to the laws administered by FDA.

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

FDA uses a variety of tools[5] for oversight of FDA-regulated products and establishments. During the COVID-19 pandemic, FDA used RRAs to help the Agency conduct oversight, mitigate risk, and meet critical public health needs with respect to certain FDA-regulated products. RRAs have included: (1) mandatory RRAs involving review of records or other information submitted by certain establishments upon request from FDA under section 704(a)(4) of the FD&C Act and review of records from food establishments subject to FD&C Act section 805[6] (the latter hereinafter referred to as "requests for Foreign Supplier Verification Program (FSVP) records under 21 CFR 1.510(b)(3) or 1.512(b)(5)(ii)(C)"); and (2) voluntary RRAs involving remote requests for records and/or interactive evaluations (such as remote livestreaming video of operations, teleconferences, and screen sharing).

FDA's experiences have identified significant benefits in using RRAs. For instance, RRAs have assisted FDA in verifying corrective actions taken in response to inspections of previously compliant

[3] See, e.g., FDA's November 2021 "An Update to the Resiliency Roadmap for FDA Inspectional Oversight," where we reported on the use of RRAs as a tool to fortify FDA oversight efforts throughout the pandemic.
[4] See, e.g., question A.2. describing to whom voluntary and mandatory RRAs may apply.
[5] See, e.g., the discussion of alternative tools used for oversight listed in FDA's May 2021 "Resiliency Roadmap for FDA Inspectional Oversight," and Section 704 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 374).
[6] Section 805 of the FD&C Act requires importers as defined for purposes of section 805 of the FD&C Act to perform certain risk-based Foreign Supplier Verification Programs (FSVP) activities. Further, section 805(d) of the FD&C Act provides for FSVP records to be made available promptly to the FDA upon request. The FSVP regulation states that, if requested in writing by FDA, records must be sent to FDA electronically, or through any other means that delivers the records promptly, rather than making them available for review at an importer's place of business. 21 CFR 1.510(b)(3), 1.512(b)(5)(ii)(C).

manufacturers[7] and in gaining compliance insight when it was not practicable to inspect. RRAs have also provided information about deficient practices, leading FDA to take regulatory actions and/or conduct inspections, as well as informing future inspection planning. RRAs were used to help support review and promote timely approval or authorization of marketing submissions for FDA-regulated products. In the food program, RRAs have assisted in determining compliance with veterinary feed directive regulations, assessing foreign manufacturing process records, adding foreign establishments to import alerts, and issuance of warning letters.

Based on these experiences, FDA has determined that RRAs are valuable and, therefore, under certain circumstances, should be continued to assist FDA in its mission to protect public health, oversee regulated industry, and ensure all types of regulated products comply with FDA requirements.

With respect to section 704(a)(4), this provision of the FD&C Act, including as recently amended by the Food and Drug Omnibus Reform Act of 2022 (FDORA),[8] gives FDA authority to request (and requires establishments to provide) any records or other information that FDA may inspect under section 704 of the FD&C Act, in advance of or in lieu of inspections of such establishments that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or device,[9] or a site or facility that is subject to inspection under section 704(a)(5)(C) (i.e., sites, entities, or facilities subject to bioresearch monitoring (BIMO) inspections).

The Agency believes that FDA's use of both mandatory and voluntary RRAs, as applicable, for all types of FDA-regulated products is in the interest of the public health, and the Agency is issuing this guidance to provide further transparency to stakeholders about the circumstances in which mandatory and voluntary RRAs may be used.

The Agency is also issuing this guidance to promote greater consistency in the way RRAs are conducted, including explaining processes for responding to an RRA request, and outlining factors we use for evaluating whether an establishment has responded timely and appropriately to a mandatory request.

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[7] In instances where FDA has identified objectionable conditions regarding compliance with laws and regulations enforced by FDA (e.g., Current Good Manufacturing Practice requirements for FDA-regulated products), FDA may subsequently determine compliance based on a voluntary commitment of corrective actions, or, when warranted, FDA may pursue a regulatory action. If FDA pursues a regulatory action after conducting an RRA, we generally will conduct an inspection to confirm that corrective actions have been implemented; however, for certain regulatory actions and with respect to select instances involving certain programs, FDA could determine that an RRA is appropriate.

[8] FDORA was enacted as part of the Consolidated Appropriations Act, 2023, Pub. L. No. 117-328 (2022). FDORA sections 3611(b)(1)(A) and 3612(a) added device and bioresearch monitoring establishments as establishments that are subject to mandatory requests for records or other information under section 704(a)(4) of the FD&C Act (21 U.S.C. 374(a)(4)).

[9] The terms "drug" and "device" are defined at FD&C Act sections 201(g)(1) and (h), respectively. With respect to drugs, a "drug" includes human and animal drugs (including all compounded human and animal drugs), and biological drug products for humans.

III. Questions and Answers

This section is intended to provide FDA's current thinking regarding the requesting, conducting, and use of RRAs by FDA.

A. Remote Regulatory Assessment Fundamentals

1. What is an RRA?

An RRA is an examination of an FDA-regulated establishment and/or its records, conducted entirely remotely, to evaluate compliance with applicable FDA requirements. RRAs assist in protecting human and animal health, informing regulatory decisions, and verifying certain information submitted to the Agency.

RRAs are a tool FDA may use to support regulatory decisions and oversight activities. Mandatory RRAs are conducted under legal authorities mandating the establishment's participation. Requests for records or other information from establishments subject to section 704(a)(4) of the FD&C Act, and requests for FSVP records under 21 CFR 1.510(b)(3) and 1.512(b)(5)(ii)(C), are included among RRAS that are mandatory. RRAs that are not conducted under statutory or regulatory authorities mandating an establishment's participation are voluntary in that an establishment can decline to participate or withdraw participation during the RRA, in which case the Agency may consider other tools for evaluating compliance with FDA requirements.

RRAs complement FDA's authority to conduct inspections under section 704(a)(1) of the FD&C Act and other applicable FDA authorities. RRAs do not limit the authority of FDA to conduct inspections under section 704(a)(1) of the FD&C Act and other applicable FDA authorities.

2. Who may be subject to an RRA?

- *Mandatory RRAs*

Mandatory RRAs include those conducted for: (1) establishments that are subject to section 704(a)(4) of the FD&C Act[10]; and (2) importers, as defined in 21 CFR 1.500, that are subject to FSVP under section 805(d) of the FD&C Act and implementing regulations in 21 CFR 1.510(b)(3) or 1.512(b)(5)(ii)(C), as applicable.[11]

[10] As described above, section 704(a)(4)'s mandatory records request authority applies to drug and device establishments and to sites, entities, or facilities subject to BIMO inspections. See footnote 8 for information on recent amendments that made device establishments and BIMO sites, entities, and facilities subject to mandatory records request authority under section 704(a)(4) of the FD&C Act.

[11] As discussed above, RRAs have included these mandatory remote requests for records or other information. Although they are discussed in this draft guidance in response to certain frequently asked questions, RRAs conducted under section 704(a)(4) or under FSVP are not necessarily the only types of mandatory RRAs for which FDA has authority.

Upon initiating a mandatory RRA, FDA intends to make clear the authorities under which the RRA is being requested.

- *Voluntary RRAs*

If an RRA is not mandated by statute or regulation (or FDA opts against exercising its mandatory RRA authority in a certain instance), FDA may request that any establishment (e.g., food producers, tobacco product manufacturers, drug or medical device manufacturers[12,13], clinical investigators, or others) participate in a voluntary RRA.

3. Are RRAs replacing other established means of obtaining information outside of inspections?

No, RRAs are not intended to limit or replace other established means of obtaining information necessary for FDA to accomplish its public health mission outside of inspections, including, among other things, applicant information request letters, registration confirmations, meetings, product submission, application assessments, or follow-up communications during outbreaks or other emergencies. Similarly, if, for example, FDA calls an applicant to inform them that a submission or application is missing certain information, this is not an RRA. Although these activities may be conducted remotely, the Agency does not consider these RRAs.[14]

4. Is an RRA an inspection?

An RRA is not an inspection under sections 704(a)(1) or 704(a)(5) of the FD&C Act. Generally, an inspection, such as described in section 704(a)(1) of the FD&C Act, involves duly designated officers or employees of the FDA physically entering (at reasonable times and in a reasonable manner), establishments subject to regulation under the FD&C Act to determine compliance with applicable requirements.[15]

However, because remote requests for FSVP records are under the authority of section 805(d) of the FD&C Act and FDA's implementing regulation, these record requests function as inspections in that FDA uses these records requests to evaluate a food importer's compliance with FSVP.

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[12] In this draft guidance, references to drug and device manufacturers means establishments that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or device, respectively. See, e.g., section 510 of the FD&C Act and 21 CFR 207.1 and 807.3.

[13] By virtue of applying to both drug and device establishments, section 704(a)(4) of the FD&C Act also applies to establishments that manufacture, prepare, propagate, compound, or process combination products (see section 503(g)(1)(C) of the FD&C Act) and the drug and device constituent part(s) (defined under 21 CFR Part 4) of such combination products. Establishments that engage in the manufacture, preparation, propagation, compounding, or processing of combination products that are not subject to the authorities under section 704(a)(4) of the FD&C Act may voluntarily participate in an RRA.

[14] FDA intends to clearly indicate when we consider an activity to be an RRA so establishments can differentiate RRA interactions from non-RRA interactions.

[15] FD&C Act, section 704(a)(1). Relatedly, for requests for records and other information under section 704(a)(4), FDA does not intend to issue a Form FDA 482, Notice of Inspection or Form FDA 483, Inspectional Observations during the RRA process.

5. When may FDA initiate or request to conduct an RRA?

FDA may initiate or, in the case of a voluntary RRA, request to conduct, an RRA whenever we determine an RRA is appropriate to help fulfill the Agency's regulatory responsibilities and protect human and animal health. For example:

- When FDA cannot conduct an inspection due to travel limitations brought on by public health emergencies, natural disasters, or other situations making travel infeasible.
- When FDA determines that an RRA will assist us in conducting elements of establishment oversight or support regulatory decisions. Examples include preparing for an already planned inspection, following up on a consumer complaint, assisting in verifying that an establishment has completed certain corrective actions (e.g., in response to a previous inspection, or previous RRA), or supporting the review of a marketing submission.

FDA intends to use a risk-based approach to determine whether to initiate or request an RRA. Factors that may be considered include, but are not limited to, establishment location, inspection history, complexity of product and process, and travel restrictions. Programs and centers within FDA may assess risk differently based on those factors.

The above examples are illustrative, and the ultimate decision to initiate or request an RRA rests with FDA, as we retain discretion to deploy RRAs as appropriate. FDA does not accept requests to perform an RRA. When FDA determines an inspection (as opposed to an RRA) is necessary, FDA intends to perform an inspection.

6. Will FDA use RRAs during or as part of an FDA inspection of an establishment?

No, FDA does not plan to conduct RRAs and inspections[16] of an establishment under sections 704(a)(1) or 704(a)(5) of the FD&C Act simultaneously. An RRA is conducted remotely by FDA staff without FDA staff present at an establishment conducting an inspection. However, an RRA could precede, prompt, or be a follow-up to, an inspection. When an RRA precedes an inspection, FDA will generally conclude the RRA prior to initiating the inspection. FDA may combine any information gained from the RRA with any resulting observations from the subsequent inspection. In such circumstance, FDA would confirm any observations from the RRA during the subsequent inspection before including them on any Form FDA 483 Inspectional Observations issued at the conclusion of the subsequent inspection.

Additionally, FDA may conduct an RRA following an inspection in order to conduct follow-up activities with the establishment or to assist in verifying corrective actions, if appropriate.

FDA may decide to conduct an RRA (e.g., livestreaming) during oversight activities independently conducted by state or foreign regulatory partners.[17]

[16] FDA considers inspections that are done with state officers or employees duly commissioned under 702(a)(1)(A) of the FD&C Act to be FDA inspections for the purposes of this draft guidance.
[17] Generally, FDA does not intend to conduct RRAs during Medical Device Single Audit Program (MDSAP) audits.

7. What are the benefits of an RRA?

FDA, industry, and the general public can all benefit from RRAs as RRAs help the Agency to meet critical public health needs. These potential benefits may include, but are not limited to:

- Allowing FDA to remotely evaluate compliance of FDA-regulated products, clinical studies, and establishments, as appropriate. This may identify issues that lead establishments to promptly make corrective actions, which may enhance the establishment's preparedness for their next FDA inspection.
- Having an RRA precede an inspection under section 704(a) of the FD&C Act could reduce resource expenditure. For example, FDA may not need to review as many records during the inspection, reducing the time FDA is present at the establishment.
- Helping to support timely regulatory decisions (including the approval of an application or authorization for emergency use), without an inspection, when appropriate conditions are fulfilled, such as the ability to verify information in the marketing submission. In such cases, the application approval, or the authorization, must still meet applicable standards.
- Providing FDA additional information to incorporate into a risk-based inspection schedule, thereby helping FDA use inspectional resources more efficiently and effectively.
- Assisting FDA in verifying corrective actions.[18]

B. Remote Regulatory Assessment Expectations

8. How may FDA request an RRA?

FDA may use multiple processes for requesting voluntary or initiating mandatory RRAs.[19]

- *In general, for Voluntary RRAs*
    - FDA expects to contact an establishment through the establishment's point of contact,[20] by email or phone, once we determine an RRA is appropriate based on FDA mission needs.

[18] See footnotes 2 and 7.

[19] When finalized, this draft guidance will represent the Agency's current thinking on how RRAs apply generally to all FDA-regulated products. Other Agency documents may exist that provide additional information about RRAs with respect to specific circumstances. See, e.g., FDA Staff Manual Guide 9004.1, Policy and Procedures for Requesting Records in Advance of or in Lieu of a Drug Inspection; FDA Compliance Program Guidance Manual 7303.878, FSVP Inspections; Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities, Draft Guidance for Industry, October 2023.

[20] FDA will typically request to speak with an establishment's owner, operator, or agent in charge at the site (i.e., top management official at the site), or their designee.

- FDA may use the establishment's registration, establishment information provided in a marketing submission, or additional information available to FDA, to identify the point of contact, authorized official, or U.S. agent.
- FDA will obtain the establishment's consent to the RRA before we begin the RRA. Where practicable, FDA generally intends to seek to obtain such consent in writing. This typically includes:
  - notifying the establishment's point of contact of the purpose and planned scope of the RRA and of the right to refuse consent; and
  - requesting that such person confirm the establishment voluntarily consents and has the ability to participate in the voluntary RRA requested.
- If the establishment consents to the voluntary RRA, FDA will typically provide an opportunity to discuss, as applicable and appropriate:
  - FDA's expectations for, and any establishment limitations in participating in, the RRA.
  - The scheduling of virtual interviews and meetings.
  - Technological capabilities.[21]
  - The process and timeline for requesting records or other information for review.
  - How and when FDA will provide feedback to the establishment.
  - Any questions relating to the process or other aspects of the RRA.

- *In general, for Mandatory RRAs*
  - FDA will initiate the request in accordance with the relevant legal authority and intends to follow any established procedures.
    - For example, for purposes of section 704(a)(4) of the FD&C Act, FDA will use Form FDA 4003 (for drug establishments) or a similar method for other establishments subject to section 704(a)(4) to request records or other information.[22] When making a section 704(a)(4) request, FDA will, under this statutory authority, provide a sufficient description of the records or other information requested, as well as our rationale for requesting such records or other information in advance of, or in lieu of, an inspection.[23]

[21] Any technical requirements, as applicable, will be discussed between FDA and the establishment prior to or during an opening meeting. In conducting the RRA, FDA will determine best logistical approaches and/or technology methods, as applicable, in coordination with the establishment.
[22] The point of contact listed in the registration may be used as the point of contact. For pre-approval and pre-licensing inspections, there may be situations when records are requested of an establishment under section 704(a)(4) of the FD&C Act related to products named in multiple applications. In these situations, FDA intends to issue one Form FDA 4003 to the establishment to cover requests for records or other information for all of the products in the applications being assessed.
[23] See section 704(a)(4)(A) of the FD&C Act, as amended by FDORA.

Upon receipt of the requested records, we will provide confirmation of receipt to the establishment.[24]

- Under 21 CFR 1.510(b)(3) and 1.512(b)(5)(ii)(C) for imported foods, FDA uses Form FDA 482d to request FSVP records.

Regardless of whether an RRA is mandatory or voluntary, FDA does not intend to issue a Form FDA 482, Notice of Inspection as part of the RRA process.[25]

9. What might an establishment expect to happen during an RRA?

RRAs may entail, but are not limited to, any combination of the following, depending on the type of RRA involved:

- FDA requests and reviews records and other information (such as electronic systems, and source records from non-clinical and clinical studies).
- Virtual meetings between FDA and responsible establishment personnel to review, where appropriate, the information provided to FDA, the establishment's electronic systems, the establishment's operations, and/or the establishment's standard operating procedures. Interactions beyond the virtual meeting between FDA and an establishment may continue during the course of an RRA.
- Use of livestream and/or pre-recorded video, where appropriate, to examine facilities, operations, data, and other information.

FDA may review electronic systems and source records by screen sharing and livestream/video.[26] FDA may provide updates to the establishment on observations and outstanding issues, whenever feasible, throughout the RRA. FDA expects to make reasonable and appropriate efforts to discuss observations with the management of the establishment, to minimize surprises, errors, and misunderstandings.

While mandatory RRAs that are conducted under their respective relevant authorities involve activities detailed by such authorities, an establishment could agree to participate in activities beyond what is required. For instance, FDA may request that an establishment subject to a section 704(a)(4) records request instead voluntarily participate in an RRA that accommodates review through interactive technologies such as video streaming.

[24] See section 704(a)(4)(B).
[25] See footnote 15.
[26] FDA does not intend to record RRAs conducted via livestream, video, or screen sharing; however, FDA may request records we review during those sessions.

10. Are there any consequences for declining to participate in an RRA?

- *Voluntary RRAs*

Because of the voluntary nature of these assessments, declining to participate in a voluntary RRA will not result in any enforcement action by the Agency based on the declination.[27] FDA may consider other activities necessary to exercise our oversight responsibilities regarding that establishment, such as an inspection, based on considerations such as when the establishment was last inspected, our assessment of risks, and other relevant factors. An establishment may decline to participate in a voluntary RRA, but an establishment may not opt out of an FDA inspection.

Moreover, if an establishment declines FDA's request to conduct a voluntary RRA, FDA may not be able to assess the establishment's activities until we exercise other oversight tools. Indeed, a voluntary RRA may be the most expedient means for FDA to assess the establishment, especially when factors prevent FDA from conducting a timely inspection. For example, in circumstances which temporarily limit FDA's ability to conduct an inspection, such as travel restrictions, it may take FDA longer to assess an establishment or, for example, a marketing submission in which an establishment is referenced, absent an RRA because we lack necessary information.

- *Mandatory RRAs*

FDA may deem the following actions, among others, as declining to participate in a mandatory RRA: failing to respond, withdrawing participation, and refusing to provide records upon a lawful request. There are consequences for declining mandatory RRAs. For example, an establishment that refuses a request for records or other information under section 704(a)(4) of the FD&C Act may be in violation of the FD&C Act.[28]

Similarly, if an importer refuses FDA's written request for FSVP records under 21 CFR 1.510(b)(3) or 1.512(b)(5)(ii)(C), the importer may be in violation of section 805 of the FD&C Act, and the food offered for import by the importer may be subject to refusal under section 801(a)(3) of the FD&C Act.[29]

FDA intends to take appropriate action against persons[30] and products that are in violation of the FD&C Act.

11. Are there any technological expectations for an RRA?

The technological expectations will vary depending on the type of RRA and its scope. Certain RRAs involve records requests, and the records may be submitted electronically or through other means. Other RRAs may require additional technological capability. For example, if FDA expects that the RRA could include the use of live streaming video, FDA may inquire about hardware or internet connectivity to assess IT operability, security, and privacy controls to protect the confidentiality of the data. The quality

[27] This would not be considered a refusal for purposes of section 301(e) or (f), or 807, of the FD&C Act.
[28] See e.g., section 301(e) of the FD&C Act (Prohibited Acts).
[29] 21 CFR 1.514(a).
[30] See section 201(e) of the FD&C Act (Definitions).

of the remote connection (e.g., connectivity, image quality, cameras used) should be adequate for FDA to review, observe, examine, and evaluate the requested records, documents, and other information (including electronic systems). To the extent practicable, technologies employed should also allow access for remotely viewing and evaluating operations at the establishment, as appropriate (e.g., aseptic practices, equipment cleaning and set up, material weighing and dispensing, instrument set up, sampling, and testing).

If an establishment is unable to support streaming video or other live virtual interactions, or if FDA determines that the streaming video or any other virtual interaction during the RRA does not permit a sufficient examination of the establishment or of a corrective action, FDA may use other available tools or may terminate the RRA and consider other actions necessary to exercise our oversight responsibilities regarding that establishment, such as an inspection.

Recommendations for sending records or other information are further explained in question 15, below.

C. Requests for Records or Other Information as Part of Remote Regulatory Assessments

12. What records or other information may FDA request as part of an RRA?

For voluntary RRAs, FDA may request records or other information appropriate to determine whether an establishment or FDA-regulated product or clinical study is in compliance with applicable requirements. The records and other information will typically be similar to what FDA would request during an inspection under section 704(a)(1) of the FD&C Act.

In the case of mandatory RRAs, the records or other information we request, and the circumstances under which we request them, will conform to the relevant legal authority. For example, under section 704(a)(4) of the FD&C Act, FDA may request any records or other information subject to inspection under section 704. For mandatory RRAs under 21 CFR 1.510(b)(3) and 1.512(b)(5)(ii)(C), FDA may request any and all records that are required to be maintained under 21 CFR 1, Subpart L.

Examples of records or other information the Agency may request during a voluntary or mandatory RRA include, but are not limited to:

- Records of specific production lots or batches as well as product-specific information, such as periodic product reviews,[31] product quality reports, equipment records, process validation records and reports, test results, records of product postmarket defects or other information related to compliance with Current Good Manufacturing Practice requirements.
- Certain summaries or lists of records, such as a summary of batches manufactured and their disposition, or a summary of discrepancies and investigations related to manufacturing and testing.

[31] See 21 CFR 211.180(e).

- Read-only access to electronic databases[32] or a request that an establishment walk us through information in their database or provide data queries or summary data generated by the establishment from their databases.
- Standard Operating Procedures and records generated by the establishment to document control of quality systems and/or to demonstrate compliance with the applicable FDA requirements.
- For FSVP importers, records related to hazard analysis, the importer's determination of appropriate supplier verification activities, performance of supplier verification activities, and/or corrective actions.
- For establishments subject to BIMO inspection, records or data related to the reporting or conduct of FDA-regulated research.

Where applicable, FDA intends to take appropriate efforts to minimize the quantity of records or other information requested and may request that establishments take reasonable efforts to facilitate and expedite FDA's collection and review of records. See questions 14 and 15 for additional details.

13. For what purposes may FDA use the records and other information gathered during an RRA?

Depending on the scope of the RRA, the information and documentation may be used by FDA for, among other things,[33] the following regulatory purposes:

- Support FDA's assessment of pending marketing submissions, including whether to approve an application or whether to issue a response, such as a complete response letter.[34]
- Determine whether an establishment or product is or is not in compliance with certain FD&C Act or PHS Act requirements, and other applicable requirements.
- Facilitate assessment of the need for an inspection in follow-up to a reported concern or defect.
- Support actions such as a regulatory meeting, warning letter, import action, recall activity, or other advisory action, or to support an administrative or judicial action.
- Determine the priority of establishments for inspection, particularly a surveillance inspection.

[32] See FDA Investigations Operations Manual (IOM) 5.10.2.1.
[33] See, e.g., section 704(a)(4)(C) of the FD&C Act, as added by FDORA.
[34] A complete response letter is either "a written communication to an applicant from FDA usually describing all of the deficiencies that the Agency has identified in a new drug application or abbreviated new drug application that must be satisfactorily addressed before it can be approved" (21 CFR 314.3); or "a written communication to an applicant from FDA usually describing all of the deficiencies that the agency has identified in a biologics license application or supplement that must be satisfactorily addressed before it can be approved" (21 CFR 600.3(ll)); see also 21 CFR 314.110 and 21 CFR 601.3.

14. If the RRA requests records or other information, what is the timeframe for submitting the records and other information to FDA?

For mandatory RRAs, FDA will request that records and other information be submitted within a timeframe consistent with the relevant legal authority.[35] For voluntary RRAs, FDA may suggest timeframes to ensure the RRA is completed in a reasonable amount of time and expects establishments to work diligently to provide the requested records and other information.
The circumstances that relate to FDA's expectations for reasonable request timeframes may include:

- The size, available resources, and capabilities of the establishment, including those that might exist for small businesses.
- The type, complexity, and volume of the records and other information being requested.
- The reason for the request, such as an application action goal date, deadline, or other time-sensitive reasons.
- Need for translation of records.

15. How should records or other information in response to an RRA request be provided to FDA?

Except as provided below, requested records or other information generally should be submitted in an electronic format. FDA intends to provide a secure means to send requested records and information. For electronic documents, establishments should identify any limitations on external access and ensure that encrypted and password-protected files can be accessed by FDA. FDA will follow applicable federal law governing the confidentiality of records and information submitted to the Agency (see, e.g., 5 U.S.C. 552(b)(4), 18 U.S.C. 1905, 21 C.F.R. Part 20).

FDA recognizes that some establishments maintain documents in paper format. Requested documents maintained in paper format should be scanned as searchable Portable Document Format (PDF) files, when possible, and sent by the secure means identified by FDA. If a paper format is the only option for sending copies of records, FDA will provide the name and contact information of the FDA staff member to whom the records should be sent.

[35] For example, for RRAs under section 704(a)(4) of the FD&C Act, persons subject to the request must provide the requested records or other information within a reasonable timeframe, within reasonable limits, and in a reasonable manner. See Section 704(a)(4)(A). See also FDA's Staff Manual Guide, 9004.1, Policy and Procedures for Requesting Records in Advance of or in lieu of a Drug Inspection for more information on timeframes. For RRAs under section 805(d) of the FD&C Act, persons subject to the request must provide the records promptly. FDA generally expects FSVP records to be sent within 72 hours of the request. See FDA's Guidance for Industry: Foreign Supplier Verification Programs for Importers of Food for Humans and Animals, available here: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-foreign-supplier-verification-programs-importers-food-humans-and-animals.

FDA may request that records and other information be in English or accompanied by an English translation.[36] If translated, the translation should be complete and accurate, and, when applicable, should include the name, address, and a brief statement of the qualifications of the translator. Copies of the original records and information should also be included in the response, where appropriate. For certain RRAs, if a verified translation is not immediately available, FDA may request that the initial translation be followed up with a verified translation as soon as practicable.

If the records or other information are provided as part of a section 704(a)(4) request, the records and information may be submitted in either electronic or physical form. FDA will provide confirmation upon receipt of the records. [37] In general, FDA intends to maintain open communications to discuss any records received over the course of the RRA.

For RRAs under 21 CFR 1.510(b)(3) and 1.512(b)(5)(ii)(C), records must be sent electronically, or through any other means that delivers the records promptly upon written request from FDA.

D. Completion of a Remote Regulatory Assessment

16. What may occur upon completion of an RRA?

Upon completion of an RRA, FDA may have a closeout meeting[38] with the establishment's management. At the closeout meeting, FDA may present a written list of RRA observations, if any, and describe and discuss such observations in sufficient detail to enable understanding and foster an appropriate response. For purposes of this guidance, RRA observations are defined as conditions and/or practices observed during the RRA that indicate, in the judgment of the FDA employee(s) conducting the RRA, a potential violation of the laws enforced by FDA. FDA does not intend to issue a Form FDA 483, Inspectional Observations, for an RRA.[39] (See question 6 for a discussion of how observations from an RRA may be confirmed during an inspection and included on a Form 483).

An establishment should be aware that a written list of observations may be subject to a request under the Freedom of Information Act at the time the disclosure to the establishment is first made (see 21 CFR 20.101(a)) and may be made publicly available, with applicable redaction of information that is exempt from public disclosure (see, e.g., 5 U.S.C. 552(b), 18 U.S.C. 1905, 21 U.S.C. 331(j), 360j(c), 360nn(e), and 387f(c), and 21 C.F.R. Part 20).

FDA encourages establishments to respond during the meeting, and/or provide written responses to the observations within fifteen (15) U.S. business days. Responses or corrective actions submitted to FDA during that timeframe in response to the issues identified during the RRA generally will be considered

[36] For RRAs of FSVP importers, upon FDA request, the importers must provide within a reasonable time an English translation of records maintained in a language other than English. See 21 CFR 1.510(b)(1), 1.512(b)(5)(C)(ii)(A).
[37] Section 704(a)(4)(B) of the FD&C Act.
[38] There may be some instances where a closeout meeting may not happen, such as for some requests under section 704(a)(4) of the FD&C Act. In such circumstances, FDA intends to notify the establishment that the RRA is concluded, along with any pertinent information**.**
[39] FDA will use a Form FDA 483a, FSVP Observations, to issue observations to an importer based on RRAs that are FSVP record reviews under 21 CFR 1.510(b)(3) and 1.512(b)(5)(ii)(C).

before further Agency action or decision. Establishment responses are available for public disclosure as described in 21 CFR 20.103 with redaction of non-public information, as appropriate.

FDA's written list of RRA observations is not a final Agency action or decision. However, evidence collected in the course of an RRA may be used in support of such actions or decisions.

Following an RRA, FDA may conduct an inspection. FDA may consider other actions, as appropriate, including an enforcement action.

As part of the RRA process, FDA intends to ordinarily prepare a report consisting of a narrative and supporting documents that communicates the summary of information reviewed, conditions and practices found, and the observations identified. FDA generally expects to provide a written copy of the narrative portion of the RRA report[40] to the establishment, following the determination that the RRA is closed (see 21 CFR 20.64(d)(3)). At that time, the report and supporting documents, with any applicable redactions, also become available for public disclosure upon request.

[40] There may be some instances where a report may not be written or provided, such as when the requested records under section 704(a)(4) of the FD&C Act were used to prepare for an inspection or for some requests for FSVP records under 21 CFR 1.510(b)(3) and 1.512(b)(5)(ii)(C).

Contains Nonbinding Recommendations
Draft-Not for Implementation

Insanitary Conditions in the Preparation, Packing, and Holding of Tattoo Inks and the Risk of Microbial Contamination: Guidance for Industry

Draft Guidance

This guidance is being distributed for comment purposes only.

Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that FDA considers your comment on this draft guidance before we begin work on the final version of the guidance, submit either electronic or written comments on the draft guidance within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2023-D-1083 listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-1130.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

June 2023

Table of Contents

Insanitary Conditions in the Preparation, Packing, and Holding of Tattoo Inks and the Risk of Microbial Contamination: Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

Under section 601(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 361(c)), a cosmetic is deemed to be adulterated if it "has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health." Cosmetic products prepared, packed, or held under insanitary conditions could become contaminated and cause serious adverse events. The risk of such adverse events is even greater in products such as tattoo inks, which are introduced through the skin.

Tattooing has become increasingly popular in the United States. Polling and data suggest that about 30 percent of all Americans, and 40 percent of those aged 18-34, have at least one tattoo (Refs. 1 and 2). State and local jurisdictions generally regulate the practice of intradermal tattooing, including permanent makeup. FDA regulates, among other things, the inks used in that practice.[2] Tattoo inks are cosmetics as defined by section 201(i) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 321(i)) because they are articles intended to be introduced into or otherwise applied to the human body for beautifying, promoting attractiveness, or altering the appearance.

FDA is issuing this guidance to help tattoo ink manufacturers and distributors recognize situations in which a tattoo ink may become contaminated with microorganisms, and thus, be potentially injurious to health. This guidance also recommends certain steps that manufacturers and distributors could take to help prevent the occurrence of these conditions, or to identify and remediate insanitary conditions that already exist during manufacturing and distribution.

[1] This guidance has been prepared by the Office of Cosmetics and Colors and the Office of Regulations and Policy in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

[2] Pigments, which are color additives regulated by FDA, are a component of finished tattoo inks. This guidance focuses on microbial contamination of finished inks.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. Background

Human skin is composed of multiple layers, including the epidermis, or outermost skin layer that serves as the body's primary physical barrier against pathogens and other harms; and the dermis, or deeper layer that contains, among other things, blood and lymphatic vessels. Microorganisms are normally present on the epidermis, but not in deeper skin layers, such as the dermis. Microorganisms normally regarded as nonpathogenic when applied topically may become opportunistically pathogenic and virulent when introduced in other ways (e.g., in wounds or via cosmetics introduced into or through the skin).[3] The presence of microorganisms in deeper skin layers may give rise to infection and inflammation.

Tattooing involves puncturing the epidermis about 100 times per second with needles and depositing ink 1.5 to 2 millimeters below the surface of the skin, deep into the dermis (Ref. 3). It generally causes bleeding because the needles pierce the blood vessels (Refs. 4 and 5). Contaminated tattoo ink can cause infections and serious injuries. Because these inks are injected, pathogens or other harmful substances in these inks can travel from the injection site through the blood and lymphatic systems to other parts of the body. Commonly reported symptoms of tattoo ink-associated infections include injection-site rashes and other lesions, including blisters and granulomas, some of which have resulted in permanent scarring. Tattoo-associated microbiological infections can also include impetigo,[4] erysipelas,[5] cellulitis,[6] and systemic infections that can cause life-threatening complications such as endocarditis, septic shock, and multi-organ failure (Ref. 8). Indications of an infection can be difficult to recognize, as other conditions (e.g., allergic reactions or other sources of inflammation) may initially have similar signs and symptoms, leading to misdiagnosis and ineffective treatments.

We have received multiple reports of illness caused by microbially contaminated tattoo inks, and subsequent testing has found many sealed tattoo inks in the United States with microbial contamination. For instance, in 2012, contaminated tattoo inks caused a multi-state outbreak of nontuberculous mycobacterial skin infections (Ref. 9). Nontuberculous mycobacterial skin infections can produce a range of symptoms, from mild inflammation (e.g., rash, papules,

[3] See Subpart J, "Microbiological Findings," in Bacteriological Analytical Manual, Chapter 23: Methods for Cosmetics, available at https://www.fda.gov/food/laboratory-methods-food/bam-chapter-23-methods-cosmetics (accessed January 5, 2022).

[4] Impetigo is a contagious superficial pus-forming bacterial infection which begins with a superficial blister that ruptures and forms a yellowish crust (Ref. 6).

[5] Erysipelas is a specific, acute, superficial infection of the skin caused by bacterium and characterized by hot, red, swollen, thickened, and sharply defined eruptions (Ref. 6).

[6] Cellulitis is a common bacterial skin infection that causes redness, swelling, and pain in the infected area of the skin. If untreated, it can spread and cause serious health problems (Ref. 7).

nodules) to severe abscesses requiring extensive and multiple surgical debridements[7] and antimicrobial therapies. Between 2003 and 2019, tattoo ink firms conducted 15 voluntary ink recalls, 14 of which resulted from findings of microbial contamination. Eight of these recalls (Refs. 11-16) occurred after FDA conducted multiple surveys of tattoo inks available in the U.S. market and tested them for microbial contamination. Many of these inks were heavily contaminated with a variety of microorganisms, some of which (such as *Pseudomonas aeruginosa* and *Bacillus cereus*) can cause serious infections (Refs. 16 and 17). In 2018, an article in the *Journal of Applied Microbiology* reported that 49 percent of the surveyed tattoo inks on the U.S. market were contaminated with microorganisms (Ref. 17). In 2019, we alerted consumers, tattoo artists, and retailers of the potential for serious injury from use of certain tattoo inks contaminated with bacteria, and we worked with manufacturers and retailers to remove the products from the market (Ref. 16).[8]

Facilities where tattoo inks are prepared, packed, or held are responsible for ensuring that the tattoo inks are not prepared, packed, or held under insanitary conditions whereby the tattoo ink may become contaminated with filth, or whereby it may have been rendered injurious to health. Tattoo inks prepared, packed, or held under such conditions are adulterated under the FD&C Act. Therefore, upon identification, such insanitary conditions would need to be remediated.

III. Discussion

A. General Considerations

In evaluating whether tattoo inks are adulterated because they have been prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth, or whereby they may have been rendered injurious to health, we generally consider the following factors:

- Tattoo inks are used by a wide variety of consumers. Therefore, when evaluating the potential harms associated with tattoo inks, we consider use by any person, including anyone who may be immunocompromised or have other relevant underlying medical conditions.

- Tattoo inks bypass the body's primary physical barrier against pathogens, because they are inserted below the epidermis.

- Pathogens that may cause no harm in a topical product may cause harm when inserted below the epidermis because of their type or amount.

[7] Debridement is the removal, usually via surgery, of torn, dead, or contaminated tissue (Ref. 10).

[8] Note that the Modernization of Cosmetics Regulation Act of 2022 (Consolidated Appropriations Act, 2023, Pub. L. No. 117-328, § 3502 (2022)) establishes new requirements for the reporting to FDA of serious adverse events associated with the use of cosmetic products.

B. Examples of Insanitary Conditions

The following insanitary conditions during manufacturing and distribution could render a tattoo ink injurious to health:

- Preparing or packing of tattoo inks in facilities not suitable for such activities (e.g., spaces that are difficult to clean and sanitize, such as carpeted areas);

- Ink, ink components (e.g., pigments, water, solvents), and primary packaging containers held uncovered, especially near open air ducts, potentially exposing them to airborne microbial contaminants and filth;

- The presence of ink and ink components (e.g., pigments, water, other solvents) contaminated with microorganisms;

- Ink and ink components (e.g., pigments, water, other solvents) held in containers that have not been cleaned and sanitized;

- Insanitary mixing of tattoo inks, including:

    - The use of containers and utensils that are not cleaned and sanitized; and
    - The use of containers without covers that expose in-process inks to microbial contaminants from the air;

- Lack of appropriate attire by personnel during manufacturing, including the failure to use hairnets, lab coats, aprons, gowns, masks, or gloves;

- Failure to equip employee restrooms with soap and water, or the lack of signage directing employees to wash their hands;

- Disposal of used personal protection clothing (e.g., gloves, masks, gowns) in the production area; and

- Storage of packaged products in locations that render them susceptible to contamination (e.g., around heavy buildup of dust and debris).

C. Recommendations

Manufacturers can take measures to help ensure that tattoo inks are not prepared, packed, or held under insanitary conditions whereby they may be contaminated with microorganisms, including:

- Test ink and ink components (e.g., pigments, water, other solvents) for microbial contamination or purchase these materials from suppliers that test for microbial contamination. Discard any materials that contain microorganisms of a type or at a level that may harm any consumer if present in the finished product;

- Ensure that the manufacturing process itself does not introduce microbial contamination (e.g., by conducting adequate cleaning and sanitization of manufacturing equipment, providing personal protective equipment to employees);

- Ensure that any sterilization method used is validated. For example, if products are intended to be "sterile," perform appropriate validated sterilization of the finished product;

- Ensure that any cleaning or sterilization method used does not adulterate the finished product (e.g., that irradiation causes no byproducts in the ink that could create poisonous or deleterious substances in the ink which may render it injurious to users under expected conditions of use); and

- Take corrective measures to prevent the release of any final product that microbiological testing shows contains microorganisms of a type or at a level that may harm any consumer and reexamine manufacturing and validation procedures to determine the cause of final product contamination.

We also suggest examining and, where appropriate, establishing good manufacturing practices (GMPs) or applying GMPs that pertain to cosmetics generally (see, for example, International Organization for Standardization (ISO) standard pertaining to cosmetics, ISO 22716, titled "Cosmetics – Good Manufacturing Practices (GMP) – Guidelines on Good Manufacturing Practices" (Ref. 18)).[9] We note that we intend to conduct rulemaking to establish good manufacturing practice regulations as part of the implementation of the Modernization of Cosmetics Regulation Act of 2022, which requires FDA to establish good manufacturing practice regulations that, to the extent practicable and appropriate, are consistent with national and international standards.[10]

IV. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at https://www.regulations.gov. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

[9] FDA has published a draft guidance entitled "Cosmetic Good Manufacturing Practices" (June 2013) (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-cosmetic-good-manufacturing-practices (accessed December 19, 2022)).

[10] See Consolidated Appropriations Act, 2023, Pub. L. No. 117-328, § 3502 (2022).

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*11. Food and Drug Administration, "Fusion Ink": Recall, posted November 30, 2017; available at https://www.accessdata.fda.gov/scripts/ires/index.cfm?Product=158974 (accessed January 19, 2023).

*12. Food and Drug Administration, "Radiant Colors": Recall, posted December 21, 2017; available at https://www.accessdata.fda.gov/scripts/ires/index.cfm?Product=160130 (accessed January 19, 2023).

*13. Food and Drug Administration, "Solid Ink": Recall, posted June 20, 2018; available at https://www.accessdata.fda.gov/scripts/ires/index.cfm?Product=164628 (accessed January 19, 2023).

*14. Food and Drug Administration, "Intenze Ink": Recall, posted July 31, 2018; available at https://www.accessdata.fda.gov/scripts/ires/index.cfm?Product=165649 (accessed January 19, 2023).

*15. Food and Drug Administration, "Eternal Ink": Recall, posted October 24, 2018; available at https://www.accessdata.fda.gov/scripts/ires/index.cfm?Product=167698 (accessed January 19, 2023).

*16. Food and Drug Administration, "FDA Advises Consumers, Tattoo Artists, and Retailers to Avoid Using or Selling Certain Tattoo Inks Contaminated with Microorganisms"; available at https://www.fda.gov/cosmetics/cosmetics-recalls-alerts/fda-advises-consumers-tattoo-artists-and-retailers-avoid-using-or-selling-certain-tattoo-inks (accessed January 19, 2023).

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Guidance for Industry
Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology

Contains Nonbinding Recommendations

June, 2014

Additional copies are available from:
Office of Policy
Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-4830
http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm

You may submit electronic or written comments regarding this guidance at any time. Submit written comments on the guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All comments should be identified with the docket number (FDA-2010-D-0530) listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact: Office of the Commissioner, Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, 301-796-4830.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner

June 2014

TABLE OF CONTENTS

Guidance for Industry
Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology[1]

This guidance represents the Food and Drug Administration's (FDA's or the Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

I. INTRODUCTION AND SCOPE

Nanotechnology is an emerging technology that can be used in a broad array of FDA-regulated products, including medical products (*e.g*. to increase bioavailability of a drug), foods (*e.g*., to improve food packaging) and cosmetics (*e.g*. to affect the look and feel of cosmetics). Materials in the nanoscale range (i.e., with at least one dimension in the size range of approximately 1 nanometer (nm) to 100 nm) can exhibit different chemical or physical properties, or biological effects compared to larger-scale counterparts. For example, dimension-dependent properties or phenomena may be used for functional effects such as increased bioavailability, decreased dosage, or increased potency of a drug product, decreased toxicity of a drug product, better detection of pathogens, more protective food packaging materials, or improved delivery of a functional ingredient or a nutrient in food (Refs. 1-6). These effects may derive from altered chemical, biological, or magnetic properties, altered electrical or optical activity, increased structural integrity, or other unique characteristics of materials in the nanoscale range not normally observed or expected in larger-scale materials with the same chemical composition (Ref. 7). Materials or end products may also exhibit similar properties or phenomena attributable to a dimension(s) outside the nanoscale range of approximately 1 nm to 100 nm (Refs. 27-30; see also discussion in Section II.B.5).

For the purpose of this guidance only, references to "products that involve the application of nanotechnology" or "nanotechnology products" mean products that contain or are manufactured using materials in the nanoscale range, as well as products that contain or are manufactured using certain materials that otherwise exhibit related dimension-dependent properties or phenomena. Likewise, we use the term "nanomaterial" generally to refer to both materials in the nanoscale

[1] This guidance finalizes the draft guidance, entitled "Draft Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology," which was issued in June, 2011. This guidance was prepared by FDA's Office of Policy in the Office of the Commissioner, in consultation with FDA's Center for Biologics Evaluation and Research, Center for Drugs Evaluation and Research, Center for Devices and Radiological Health, Center for Food Safety and Applied Nutrition, Center for Tobacco Products, Center for Veterinary Medicine, National Center for Toxicological Research, Office of the Chief Scientist, Office of Foods and Veterinary Medicine, Office of Regulatory Affairs, Office of Special Medical Programs, and Nanotechnology Task Force.

range and certain materials that otherwise exhibit related dimension-dependent properties or phenomena. Use of these terms is for the purpose of communicating FDA's current thinking elaborated in this document only.

As used in this guidance, the word "products" (or "FDA-regulated products") is meant to include products, materials, ingredients, and other substances regulated by FDA, including drugs, biological products, medical devices, food substances (including food for animals), dietary supplements, cosmetic products, and tobacco products.[2]

The guidance describes FDA's current thinking on determining whether FDA-regulated products involve the application of nanotechnology. This guidance is intended for manufacturers, suppliers, importers, and other stakeholders. (For convenience, the guidance will refer to these parties as "industry.") FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance documents means that something is suggested or recommended, but not required.

The application of nanotechnology may result in product attributes that differ from those of conventionally-manufactured products, and thus may merit particular examination. However, FDA (or "we") does not categorically judge all products that involve the application of nanotechnology as intrinsically benign or harmful. FDA will regulate nanotechnology products under existing statutory authorities, in accordance with the specific legal standards applicable to each type of product under its jurisdiction. We consider the current framework for safety assessment sufficiently robust and flexible to be appropriate for a variety of materials, including nanomaterials. FDA maintains a product-focused, science-based regulatory policy. Technical assessments will be product-specific, taking into account the effects of nanomaterials in the particular biological and mechanical context of each product and its intended use. As such, the particular policies for each product area, both substantive and procedural, will vary according to the statutory authorities and relevant regulatory frameworks (Ref. 8). We believe that this regulatory policy allows for tailored approaches that adhere to applicable legal frameworks and reflect the characteristics of specific products or product classes and evolving technology and scientific understanding.

This guidance provides an overarching framework for FDA's approach to the regulation of nanotechnology products. It identifies two points to consider when determining whether the FDA-regulated product involves the application of nanotechnology. An affirmative finding to either of the Points to Consider, elaborated in section II below, might suggest the need for particular attention by the Agency and/or industry to the product to identify and address potential implications for safety, effectiveness, public health impact, or regulatory status of the product.

This guidance does not address, or presuppose, what ultimate regulatory outcome, if any, will result in a particular case where the use of these points may indicate that an FDA-regulated product involves the application of nanotechnology. Issues such as the safety, effectiveness,

[2] Nanotechnology may also be applied to combination products (as defined at 21 CFR 3.2(e)).

public health impact, or the regulatory status of nanotechnology products are currently addressed on a case-by-case basis using FDA's existing review processes.[3]

This guidance also does not establish regulatory definitions. Rather, it is intended to help industry and others identify when they should consider potential implications for regulatory status, safety, effectiveness, or public health impact that may arise with the application of nanotechnology in FDA-regulated products. We advise industry to consult with FDA early in the development process to facilitate a mutual understanding of the specific scientific and regulatory issues for their nanotechnology products.

FDA will provide further guidance to industry, as needed, to address the application of nanotechnology as applicable to specific FDA-regulated products or classes of products (such as human foods, drugs, or cosmetics), consistent with existing federal policies (Refs. 9, 10). As appropriate, FDA's product-specific guidance documents will address issues such as the regulatory status, safety, effectiveness, performance, quality, or public health impact of nanotechnology products.[4]

II. DISCUSSION

FDA has not established regulatory definitions of "nanotechnology," "nanomaterial," "nanoscale," or other related terms. These terms are commonly used in relation to the engineering (i.e., deliberate manipulation, manufacture or selection) of materials that have at least one dimension in the size range of approximately 1 nanometers (nm) to 100 nm. For example, the National Nanotechnology Initiative Program defines nanotechnology as "the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications" (Ref. 11). Various published definitions mention other factors such as function, shape, charge, the ratio of surface area to volume, or other physical or chemical properties.

Based on our current scientific and technical understanding of nanomaterials and their characteristics, FDA believes that evaluations of safety, effectiveness, public health impact, or regulatory status of nanotechnology products should consider any unique properties and behaviors that the application of nanotechnology may impart. This guidance identifies two Points to Consider that should be used to evaluate whether FDA-regulated products involve the application of nanotechnology. These points address both particle dimensions and dimension-dependent properties or phenomena. Product-specific premarket review, when required, offers an opportunity for FDA to apply these points and, where products are not subject to premarket review, industry should consider these points. If either point applies to a given product, industry

[3] It bears noting that the application of nanotechnology may also affect the classification of a product. For example, nanomaterials used in medical products may function through different modes of action than larger-scale materials with the same chemical composition, which may affect the classification of the product, for example as a drug or device.

[4] FDA's guidance documents relevant to nanotechnology, including product-specific guidance documents that focus on nanotechnology applications in specific product sectors, can be found at: http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/default.htm

and FDA should consider whether the evaluations of safety, effectiveness, public health impact, or regulatory status of that product have identified and adequately addressed any unique properties or behaviors of the product.

These two Points to Consider are intended to provide an initial screening tool that can be broadly applied to all FDA-regulated products, with the understanding that these points are subject to change in the future as new information becomes available. In particular, FDA may further refine these points, either as applicable broadly to all FDA-regulated products or as applicable to particular products or classes of products, as justified by scientific information. This may include refining particle size parameters or introducing additional parameters such as those related to particle size distribution or specific properties.[5] We will consider future revisions to our approach, including developing regulatory definitions relevant to nanotechnology, as warranted and in keeping with evolving scientific understanding. As previously indicated, FDA also may provide additional guidance, including product-specific guidance documents, to address issues such as the regulatory status, safety, effectiveness, performance, quality, or public health impact of nanotechnology products.

A. Points to Consider

At this time, when considering whether an FDA-regulated product involves the application of nanotechnology, FDA will ask:

1. Whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm);

In addition, as we explain in more detail below, because materials or end products can also exhibit related properties or phenomena attributable to a dimension(s) outside the nanoscale range of approximately 1 nm to 100 nm that are relevant to evaluations of safety, effectiveness, performance, quality, public health impact, or regulatory status of products, we will also ask:

2. Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm).[6]

[5] At this time, we do not have an adequate basis on which to determine a particle number threshold or a list of "unique" or "novel" properties that are applicable across the range of FDA-regulated products. In addition, challenges related to measurement methods and biological effects add further complexity to recommending use of particle number, weight, or surface area as the most appropriate units of measure. FDA intends to actively follow scientific developments on this issue and provide additional guidance, as appropriate.

[6] As explained in section II.B.5. below, the use of 1,000 nm as a reference point should not be interpreted to mean that materials or products with dimensions above 1,000 nm cannot exhibit dimension-dependent properties or phenomena of importance to safety, effectiveness, public health impact, or regulatory status of the material or product. See further discussion on this issue in section II.B.5. below.

These considerations apply not only to new products, but also when changes to manufacturing processes alter the dimensions, properties, or effects of an FDA-regulated product or any of its constituent parts.[7]

B. Rationale for Elements within the Points to Consider

1. Material or end product that is *engineered* to have certain dimensions or exhibit certain properties (in Points 1 and 2)

The term "engineered," used in both Points 1 and 2, is used to distinguish products that have been deliberately manipulated by the application of nanotechnology from those products that contain materials that naturally occur in the nanoscale range. FDA is particularly interested in the *deliberate* and *purposeful* manipulation and control of dimensions to produce specific properties, because the emergence of these new properties or phenomena may raise questions about the safety, effectiveness, performance, quality or public health impact that may warrant further evaluation. FDA's interest in materials or products "engineered" to have nanoscale dimensions or related dimension-dependent properties or phenomena is distinct from the more familiar use of biological or chemical substances that may naturally exist at small scales, including at the nanoscale, such as microorganisms or proteins.

The term "engineered" is also used to distinguish products that have been deliberately manipulated by the application of nanotechnology from products that may unintentionally include materials in the nanoscale range.
For example, the incidental presence of particles in the nanoscale range in conventionally-manufactured products[8] is not covered under the scope of this guidance.[9]

2. Material or end product (in Points 1 and 2)

The phrase "material or end product," referred to in both Points 1 and 2, is used to cover different types of articles that are regulated by FDA, such as products, materials, ingredients, and other substances regulated by FDA. This includes finished products (e.g., a drug tablet for administration to a patient) as well as materials that are intended for use in a finished product (e.g., a food additive added to a food during processing). In determining whether a material or end product satisfies either Point 1 or Point 2, FDA will examine the material or end product, and may also consider the constituent parts of the material or end product. Therefore, relevant considerations include whether a material or end product contains or involves in its manufacture the use of materials that meet either Point 1 or Point 2.

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[7] These Points to Consider are not intended to apply to products that have been previously reviewed or approved by FDA and where no changes are made to manufacturing processes that would alter the dimensions, properties or effects of the product or its constituent parts.

[8] For example, small amounts of particles in the nanoscale range have been reported to be present in foods manufactured using conventional food manufacturing practices (Ref. 12).

[9] However, evaluations of conventionally-manufactured products may include a consideration of the effects, if any, of such incidental presence of particles in the nanoscale range on the safety, effectiveness, or public health impact of a product.

3. At least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm) (in Point 1)

A size range of approximately 1 nm to 100 nm is commonly used in various working definitions or descriptions regarding nanotechnology proposed by the regulatory and scientific community.[10] In this size range, materials can exhibit new or altered physicochemical properties that can enable novel applications (Refs. 11, 13-15). Accordingly, per Point 1, if a material or end product is engineered to have at least one external dimension in the range of 1 nm to 100 nm, or is engineered to have an internal or surface structure in the range of 1 nm to 100 nm, industry and FDA should consider any unique characteristics or biological effects exhibited by the product that may influence its safety, effectiveness, public health impact, or regulatory status. Primary particles engineered with at least one external dimension within the nanoscale range are covered in Point 1. This Point also covers any aggregates or agglomerates formed by such nanoscale primary particles. In addition, coated, functionalized, or hierarchically-assembled engineered structures that include internal or surface discrete and functional nanoscale entities, such as where such entities are embedded or attached to the surface, are encompassed within Point 1.[11] Such engineered structures with discrete and functional nanoscale entities embedded or attached to the surface may have altered properties or phenomena that may affect product safety or effectiveness (Ref. 16). The inclusion of particles, objects, or structures with internal, surface, or external dimension(s) in the nanoscale range is consistent with approaches taken by other scientific and regulatory bodies (Refs. 17-23).

4. Properties or phenomena attributable to dimension(s) (in Point 2)

While size alone, for very small particles, is suggestive of the presence of properties meriting further examination, the identification and assessment of specific dimension-dependent properties and phenomena are ultimately more relevant for purposes of FDA regulatory review and oversight. Point 2, therefore, focuses on the properties of the material and its behavior in biological systems.[12] The phrase "exhibits properties or phenomena . . . that are attributable to its dimension(s)," is used because properties and phenomena of materials in the nanoscale range enable applications that can affect the safety, effectiveness, performance, quality, public health impact, or regulatory status of FDA-regulated products. For example, as noted above, dimension-dependent properties or phenomena may be used for various functional effects such as increased bioavailability or decreased toxicity of drug products, better detection of pathogens,

[10] For example, a size range of approximately 1 nm to 100 nm is used in definitions, working definitions, or descriptions published by the National Nanotechnology Initiative (Ref. 11); Environmental Protection Agency (http://www.epa.gov/pesticides/regulating/nanotechnology.html); European Commission (Ref. 17); Health Canada (Ref. 19); International Standards Organization (Ref. 20); Organization for Economic Cooperation and Development's Working Party on Nanotechnology and Working Party on Manufactured Nanomaterials (http://www.oecd.org/sti/nano/); National Cancer Institute (http://www.cancer.gov/dictionary?cdrid=445071); and American National Standards Institute (http://nanostandards.ansi.org/tiki-index.php).

[11] This is not intended to include any incidental presence of internal or surface features with dimensions in the nanoscale range that may be present in conventionally-manufactured substances (for example, internal porosity, surface roughness or surface defects).

[12] Consistent with "Policy Principles for the U.S. Decision-Making Concerning Regulation and Oversight of Applications of Nanotechnology and Nanomaterials," Office of Science and Technology Policy, Office of Management and Budget, and Office of the United States Trade Representative, June 9, 2011 (Ref. 10).

improved food packaging materials, or improved delivery of nutrients. These effects may derive from altered or unique characteristics of materials in the nanoscale range that are not normally observed or expected in larger-scale materials with the same chemical composition (Ref. 7). However, such changes may raise questions about the safety, effectiveness, performance, quality or public health impact of nanotechnology products. In addition, considerations such as routes of exposure, dosage, and behavior in various biological systems (including specific tissues and organs) (Refs. 13, 24) are critical for evaluating the safety, effectiveness, public health impact, or regulatory status of a wide array of products under FDA's jurisdiction. Such evaluations should include a consideration of the specific tests (whether traditional, modified, or new) that may be needed (Refs. 25, 26) to determine the physicochemical properties and biological effects of a product that involves the application of nanotechnology.

5. Dimension(s) of up to one micrometer (1,000 nm) (in Point 2)

Materials or end products can also exhibit properties or phenomena attributable to a dimension(s) outside the nanoscale range of approximately 1 nm to 100 nm. Physical and chemical properties and biological behavior that are relevant to evaluations of safety, effectiveness, performance, quality, public health impact, or regulatory status of products have been observed at dimensions outside the nanoscale range of approximately 1 nm to 100 nm (Refs. 27-30). Therefore, Point 2 focuses on the importance of considering properties or phenomena attributable to dimensions, even where such dimensions may be outside the nanoscale range of approximately 1 nm to 100 nm. FDA's consideration of materials with dimension(s) outside the nanoscale range of approximately 1 nm to 100 nm is consistent with approaches taken by other scientific and regulatory organizations.[13]

[13] For example, the Joint Research Centre and the Scientific Committee on Emerging and Newly Identified Health Risks of the European Commission concluded: "In order to base a nanomaterials definition for regulatory purposes on size alone, the upper nanoscale limit should ideally be high enough to capture all types of materials that would need particular attention for regulation due to their nanoscale size. Upper limits which are often used in existing definitions, for example 100 nm, may require the introduction of one or more qualifiers based on structural features or properties other than size, in order to capture structures of concern (for example agglomerates or aggregates) with a size larger than 100 nm in the regulation" (Ref. 22); "The upper size limit for one or more external dimensions of 100 nm is complicated by the potential exclusion of aggregates, agglomerates and multicomponent assemblies that would have external sizes greater than this" (Ref. 23); and "An upper limit of 100 nm is commonly used by general consensus but there is no scientific evidence to support the appropriateness of this value (Stated as SCENIHR conclusions in the European Commission Recommendation on the definition of nanomaterial, Ref. 17). The European Commission further noted that "it may be necessary to include additional materials, such as some materials with a size . . . greater than 100 nm in the scope of application of specific legislation or legislative provisions suited for a nanomaterial (Ref. 17). In addition, the International Organization for Standardization (ISO) "acknowledged that health and safety considerations associated with intentionally produced and incidental nano-objects do not abruptly end at dimensions of 100 nm. As knowledge expands, it is abundantly clear that a robust terminology will need to capture and convey effectively the performance aspects of intentionally produced nano-objects and nanostructured materials in their definitions, apart from their fundamental size and shape" (Ref. 20). More recently, Health Canada adopted a working definition of nanomaterial that, in part, reflects that it is possible for nanoscale properties/ phenomena to be exhibited outside the 1 nm to 100 nm size range, such as select quantum devices (Ref. 19). Finally, in its second regulatory review on nanomaterials, the European Commission noted that "fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials." Several types of nanomaterials were identified as not matching the EU definition, with an acknowledgment that "there are an increasing number of particles which are engineered to have internal nanoscale features. Examples are core-shell particles and nano-encapsulates. These particles may be designed, for example for pharmaceutical applications, where the inner core particle is "released" in a certain

At the present time, available scientific information does not establish a uniform upper boundary above 100 nm where novel properties and phenomena similar to those seen in materials with dimensions in the nanoscale range cease for all potential materials or end products. For this reason, at this time, FDA finds it reasonable to consider evaluation of materials or end products engineered to exhibit properties or phenomena attributable to dimensions up to 1,000 nm, as a means to screen materials for further examination and to determine whether these materials exhibit properties or phenomena attributable to their dimension(s) and associated with the application of nanotechnology.[14] An upper limit of one micrometer (1,000 nm) applied in the context of properties or phenomena attributable to dimensions serves both to: (1) include materials with dimension(s) outside the nanoscale range of approximately 1 nm to 100 nm that may exhibit dimension-dependent properties or phenomena associated with the application of nanotechnology and distinct from those of macro-scaled materials; and (2) exclude macro-scaled materials that may have properties attributable to their dimension(s) but are not likely associated with the application of nanotechnology.

An upper limit of 1,000 nm, combined with the presence of dimension-dependent properties or phenomena similar to those seen in materials with dimensions in the nanoscale range, provides an initial screening tool to help identify materials or products with properties or phenomena of particular relevance for regulatory review. The use of 1,000 nm as a reference point in this context should not be interpreted to mean that materials or products with dimensions above 1,000 nm cannot exhibit dimension-dependent properties or phenomena of importance to safety, effectiveness, public health impact, or regulatory status of the material or product. As noted above, we may further refine these Points to Consider, including this upper limit, either as applicable broadly to FDA-regulated products or as applicable to specific products or product categories.

III. CONCLUSION

The two Points to Consider elaborated in this guidance should be applied when considering whether an FDA-regulated product involves the application of nanotechnology. An affirmative finding to either of the Points to Consider, elaborated in this guidance, might suggest the need for particular attention to the product by FDA and/or industry for potential implications for safety, effectiveness, public health impact, or regulatory status of the product. We will consider future revisions to our approach, including developing regulatory definitions relevant to nanotechnology, as warranted and in keeping with evolving scientific understanding.

There remains a need to learn more about the potential role and importance of dimensions in the physical and chemical characteristics and biological effects exhibited by FDA-regulated products

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environment. Some of these materials have an external diameter smaller than 100 nm, matching the EU nanomaterial definition, others have an external diameter larger than 100 nm, not matching the EU nanomaterial definition" (Ref. 31).

[14] However, as noted previously, FDA will consider further refinement of these Points to Consider for particular products or classes of products, as scientific information becomes available, including refining particle size parameters.

that involve the application of nanotechnology.[15] Product-specific premarket review, when required, offers an opportunity for FDA to better understand the properties and behavior of products that involve the application of nanotechnology. Where products that involve the application of nanotechnology are not subject to premarket review, we urge industry to consult with the Agency early in the product development process. In this way, any questions about the products' regulatory status, safety, effectiveness, or public health impact can be appropriately and adequately addressed. FDA has and, as needed, will continue to provide additional guidance to industry in more targeted guidance documents to address these considerations.

IV. REFERENCES

We have placed these references on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You may see them at that location between 9 a.m. and 4 p.m., Monday through Friday. As of June 1, 2014, FDA had verified the Web site addresses for the references it makes available as hyperlinks from the Internet copy of this guidance, but FDA is not responsible for any subsequent changes to Non-FDA Web site references after June 1, 2014.

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Collecting and Providing 702(b) Portions of FDA Official Samples

Questions and Answers

Guidance for Industry and FDA Staff

DRAFT GUIDANCE

This draft guidance document is for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2021-D-0593.

For questions regarding this draft document contact the Office of Regulatory Affairs (ORA), Office of Strategic Planning and Operational Policy (OSPOP) at ORAPolicyStaffs@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Regulatory Affairs
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Food Safety and Applied Nutrition
Center for Veterinary Medicine

January 2022

Contains Nonbinding Recommendations

Draft – Not for Implementation

Collecting and Providing 702(b) Portions of FDA Official Samples

Questions and Answers

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Contents

Questions and Answers Regarding Collecting and Providing 702(b) Portions of FDA Official Samples

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Draft Guidance for Industry and FDA Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

INTRODUCTION

This draft guidance is intended to assist FDA staff and industry with issues and questions related to the requirements for FDA to collect and provide portions of official samples under section 702(b) of the Federal Food, Drug, & Cosmetic Act (FD&C Act) and its implementing regulation in Title 21 Code of Federal Regulations (CFR) section 2.10 (21 CFR 2.10).

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

BACKGROUND

Section 702 of the FD&C Act (21 U.S.C. 372) authorizes FDA to conduct examinations and investigations and to collect samples.[1] Collecting samples is a critical part of FDA's regulatory activities. Under section 702(b) of the FD&C Act (21 U.S.C. 372(b)), when FDA collects a sample of a food, drug, or cosmetic for analysis, FDA must, "upon request, provide a part of such official sample for examination or analysis by any person named on the label of the article, or the owner thereof, or his attorney or agent" (hereinafter referred to as "owner"). Section 702(b) of the FD&C Act also authorizes FDA to establish, by regulation, "reasonable exceptions

[1] Courts have recognized that the plain language of section 702(b) of the FD&C Act authorizes sampling. *See*, *e.g., United States v. 75 cases, etc.*, 146 F.2d 124 (4th Cir. 1944).

from, and impose such reasonable terms and conditions relating to" the requirements of section 702(b) of the FD&C Act, as necessary for the proper administration of the provisions of the FD&C Act.

FDA's regulation at 21 CFR 2.10 was established to describe those reasonable terms and conditions to implement section 702(b) of the FD&C Act. The regulation provides a definition for official sample, states when FDA must collect and provide a part of the official sample (hereinafter referred to as the 702(b) portion) to the owner, and states when FDA may destroy the official sample, among other things. The regulation also provides exceptions to the requirement for FDA to collect and provide a 702(b) portion of an official sample to the owner.

A. TERMINOLOGY

1. What is a 702(b) portion?

FDA uses the term 702(b) portion to refer to the part of FDA's official sample of a food, drug, or cosmetic that FDA is required to provide to the owner, upon request under section 702(b) of the FD&C Act. FDA will collect and provide a 702(b) portion in accordance with 702(b) of the FD&C Act and its implementing regulation in 21 CFR 2.10.

2. What is an official sample?

A sample collected by an officer or employee of the U.S. Department of Health and Human Services (HHS) is an official sample if records or other evidence is obtained by the officer or employee or any other officer or employee of HHS indicating that the shipment or other lot of the article from which the sample is collected was introduced or delivered for introduction into interstate commerce, or was in or was received in interstate commerce, or was manufactured within a Territory as defined in section 201(a)(2) of the FD&C Act. 21 CFR 2.10(a)(1). The officer or employee of HHS must designate such sample as an official sample for it to be considered one. 21 CFR 2.10(a)(1). FDA personnel can refer to FDA's Investigations Operations Manual (IOM), Chapter 4, for instructions related to official samples.

3. What is a food, drug, or cosmetic?

The FD&C Act defines food, drug, and cosmetic in pertinent part as:

- Food means "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article" (section 201(f)); For example,

  - A dietary supplement is deemed to be food (section 201(ff))[2]
  - A food additive is a component of food (section 201(s)).
- Drug means "(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)" (section 201(g)(1)).[3]
- Cosmetic means "(1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap" (section 201(i)).

FDA occasionally performs environmental sampling (e.g. swabbing of facilities or equipment) to identify the presence of chemicals or microbes where food, drugs, or cosmetics are produced. These environmental samples do not meet the definitions of food, drug, or cosmetic.

B. QUESTIONS AND ANSWERS

1. When must FDA collect a 702(b) portion?

FDA must collect a 702(b) portion when an officer or employee of HHS collects an official sample of a food, drug, or cosmetic for analysis under the FD&C Act, unless an exception in 21 CFR 2.10(b) applies (See B.3.).

i. Must a commissioned state or local official collect a 702(b) portion when collecting an official sample?

[2] Section 201(ff)(3)(B) of the FD&C Act (21 U.S.C. 321(ff)(3)(B)) excludes from the definition of a dietary supplement a product that contains an article that was the subject of an investigational new drug exemption, new drug application, or biologics license application 1) approved as a new drug under section 505 of the FD&C Act, certified as an antibiotic under 507 of the FD&C Act, or licensed as a biologic under section 351 of the Public Health Service Act, or 2) investigated as a new drug, antibiotic or biologic for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public; and which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under the FD&C Actprior to its marketing as a dietary supplement.

[3] A biological product, as defined in section 351(i)(1) of the Public Health Service Act (PHS Act), that is also regulated as a drug under the FD&C Act's drug provisions is subject to section 702(b) (see section 351(j) of the PHS Act), as is a combination product that is subject to premarket approval under the FD&C Act's drug provisions or the PHS Act's biologics licensing provisions.

Section 702(a)(1)(A) of the FD&C Act authorizes the Secretary of HHS to conduct examinations and inspections through officers and employees of HHS or through certain officers and employees of states, territories, and political subdivisions who have been duly commissioned as an officer of HHS. Under section 702(a)(1)(A) of the FD&C Act, state and local officials duly commissioned by FDA are considered officers of HHS when conducting examinations or investigations under contract or agreement for purposes of the FD&C Act. Thus, a commissioned state or local officer or employee who collects an official sample of a food, drug, or cosmetic for analysis under the FD&C Act must collect a 702(b) portion, as required by 21 CFR 2.10(b). This guidance uses the terms "FDA staff" and "FDA investigator" to refer to an HHS officer or employee, including a commissioned state or local officer or employee.

ii. Should FDA collect a 702(b) portion if documentation of interstate commerce is not immediately available?

An FDA investigator must collect a 702(b) portion for an official sample, unless an exception applies. (See 21 CFR 2.10(a)(1) and section A.2. of this guidance for the meaning of official sample, which includes, among other things, evidence of interstate commerce.)

In some situations, such as a retail setting or as part of FDA's surveillance activities, records or evidence of interstate commerce may not be immediately available at the time of the sample collection. However, if FDA has reason to believe that the product was introduced into or in interstate commerce and expects to obtain evidence of interstate commerce at a later time, FDA should collect a 702(b) portion for the sample.

iii. What common types of samples does FDA collect that do not require a 702(b) portion?

FDA is not required to collect or provide a 702(b) portion for samples of products that are not foods, drugs, or cosmetics as defined by the FD&C Act. (21 U.S.C. 372(b); 21 CFR 2.10(b)). See section A.3 of this guidance for the definitions of food, drug, and cosmetic. For example, FDA is not required to collect a 702(b) portion for a sample that is a medical device or a tobacco product.

Other examples of samples collected by FDA that are not a food, drug, or cosmetic and thus are not subject to section 702(b) of the FD&C Act include filth exhibits that are not tied to or connected to a specific lot of product used to illustrate conditions at an establishment (e.g., rodent excreta pellets) and samples collected from equipment or surfaces to demonstrate the environmental conditions of an establishment. However, unless an exception in 21 CFR 2.10(b) applies, FDA must collect a 702(b) portion when collecting an official sample of a food, drug, or cosmetic that is associated with the filth or the environmental sample.

2. What are the exceptions to 702(b) portion collection?

An FDA investigator who is collecting an official sample of a food, drug, or cosmetic for analysis under the FD&C Act must collect at least twice the quantity estimated to be sufficient for analysis, unless one of the following exceptions in 21 CFR 2.10(b) applies:

> (1) The amount of the article available and reasonably accessible for sampling is less than twice the quantity so estimated, in which case the FDA investigator must collect as much as is available and reasonably accessible.
>
> *Considerations:* For some samples, such as when FDA is collecting an official sample from retail, rather than from the owner, the amount of the article available and reasonably accessible for sampling is less than twice the quantity estimated to be sufficient for analysis. Also, FDA may receive product from a consumer that the consumer alleges violates the FD&C Act in some respect. The consumer may have a limited portion of the article that is not sufficient to include a 702(b) portion. In these and other situations for which twice the quantity sufficient for analysis is not available, FDA should collect as much of the article that is available and reasonably accessible.
>
> (2) The cost of twice the quantity so estimated exceeds $150.
>
> *Considerations*: If the cost of twice the quantity exceeds $150, FDA investigators should consult with their supervisors (see IOM, Chapter 4).
>
> (3) The sample cannot by diligent use of practicable preservation techniques available to FDA be kept in a state in which it could be readily and meaningfully analyzed in the same manner and for the same purposes as FDA's analysis.
>
> *Considerations*: Whether the sample can be so preserved and analyzed may depend on the product from which the sample was taken. For example, some FDA products, such as fresh produce, are highly perishable and cannot be kept in a state that allows for meaningful analysis in the same manner and for the same purpose as the FDA's analysis.
>
> (4) The sample is collected from a shipment or other lot which is being imported or offered for import into the United States.
>
> (5) The sample is collected from a person named on the label of the article or his agent, and such person is also the owner of the article.
>
> (6) The sample is collected from the owner of the article, or his agent, and such article bears no label or, if it bears a label, no person is named thereon.

For exceptions (5) and (6), while FDA is not required to collect a 702(b) portion, the owners or their agents may decide at their own discretion to collect a sample to duplicate FDA's sample. Such sampling by owners or their agents is outside the scope of this guidance.

FDA may collect a 702(b) portion even if an exception applies. For example, if an official sample of an imported article, or article offered for import, is collected for use in an anticipated legal action (e.g., seizure under section 304 of the FD&C Act), FDA may collect a 702(b) portion.

3. When FDA receives a food, drug, or cosmetic as part of a consumer complaint, should FDA collect a 702(b) portion?

Yes, when collecting an official sample from a consumer as part of a consumer complaint, FDA should take reasonable efforts to collect a 702(b) portion if one is available and no exceptions apply.

4. Does FDA collect the 702(b) portion as a separate subsample?

FDA is not required to collect the 702(b) portion as a separate subsample. In some situations, when collecting, FDA may not be able to collect a separate subsample that will be used as the 702(b) portion of the official sample.

However, whenever possible, FDA may collect a separate subsample in order to provide the owner a 702(b) portion. See IOM Chapter 4. If FDA does not collect separate subsamples, FDA will collect a single sample at least twice the amount estimated to be sufficient for analysis unless an exception applies. (21 CFR 2.10(b)).

5. When must FDA provide a 702(b) portion?

21 CFR 2.10(c) establishes when FDA must provide a 702(b) portion to the owner of the sampled product. Under 2.10(c), after FDA has completed all analysis of an official sample of a food, drug, or cosmetic needed to determine whether the product is adulterated or misbranded, or otherwise subject to the prohibitions of the FD&C Act, and has reserved an amount of the article it estimates to be adequate for use as exhibits in the trial of any case that may arise based on the sample, a part of the sample, if any remains available, must be provided for analysis upon written request, by the owner, unless an exception applies.

i. If the only portion of the official sample that remains after FDA analysis is the amount reserved by FDA for use at trial, must FDA provide that portion to the owner?

No, FDA is not required to give a 702(b) portion to the owner if none remains after reserving an adequate amount for trial. Under such situations, FDA is not required to provide to the owner the portion reserved by FDA for use at trial. (21 CFR 2.10(c)).

ii. If a portion of an official sample remains after FDA analysis and reserving an amount for use at trial, must FDA provide part of the sample upon written request by the owner?

Yes, FDA must provide a portion of the official sample to the owner if any remains after reserving an amount for trial upon written request by the owner. (21 CFR 2.10(c)).

iii. If the sample was collected from a consumer as part of a consumer complaint, must FDA provide a part of the sample to the consumer?

In some consumer complaint situations, there is potential for litigation between the consumer and the firm, in addition to any action FDA may be considering. In such situations, both the firm and the consumer may request a part of the sample.

FDA is required to provide a 702(b) portion if, in part, the request is from any person named on the label of the article, or the owner thereof, or the attorney or agent of such person or owner. (21 U.S.C. 372(b)). 21 CFR 2.10(a)(3) states that the "owner of a food, drug, or cosmetic of which an official sample is collected is the person who owns the shipment or other lot of the article from which the sample is collected." FDA may consider providing a portion of a sample to a consumer who is not an owner but such portion is outside the scope of this guidance, and FDA must prioritize providing a sample to persons entitled to a 702(b) portion under the FD&C Act.

6. If FDA is required to provide a 702(b) portion, how much should FDA provide?

21 CFR 2.10(c) states, in part, that FDA must provide "a part of the sample" to the owner upon written requests, unless an exception applies. The amount of a sample that remains for providing a 702(b) portion depends on the amount of sample collected, the amount of the sample used for the analysis, and the amount of the sample reserved for trial. The amount reserved for trial is what FDA estimates to be adequate for use as exhibits in the trial of any case that may arise under the FD&C Act based on the sample and will be determined at FDA's discretion.

If it is not possible to provide the amount requested by the owner, FDA should consult with the owner to determine how much of the remaining sample the owner may want as a 702(b) portion.

7. If FDA collected one or more separate subsamples as the 702(b) portion, but the owner requests a portion of the subsample FDA used for the sample analysis, should FDA provide the portion the owner requested?

Although not required, FDA's practice is to, whenever reasonable, collect separate subsamples to serve as the 702(b) portion. Also see section B.5.

If FDA collected a separate subsample as the 702(b) portion but the owner requests a portion from the subsample FDA used for analysis, FDA may provide the owner the portion from the source requested, if any remains available after analysis and reserving an amount adequate for

use at trial. FDA Divisions receiving such requests may consult within FDA about the circumstances pertaining to the request.

8. How long should a 702(b) portion be retained?

FDA should retain the 702(b) portion until it is authorized to destroy it. Under 21 CFR 2.10(e), FDA is authorized to destroy an official sample, including the 702(b) portion, as follows:

a. FDA determines that no analysis of the sample will be made;
b. FDA determines that no notice under section 305 of the FD&C Act and no case under the FD&C Act, is or will be based on the sample;
c. The sample was the basis of a notice under section 305 of the FD&C Act and, after opportunity for presentation of views following such notice, FDA determines that no other such notice, and no case under the FD&C Act, is or will be based on the sample;
d. The sample was the basis of a case under the FD&C Act that has gone to final judgment, and FDA has determined that no other such case is or will be based on the sample;
e. The sampled article is perishable;
f. The sample is decomposed or otherwise unfit for analysis;
g. The part of the sample that will be destroyed is in excess of three times the quantity FDA estimates to be sufficient for analysis.

9. Can FDA use 702(b) portions of a sample for research purposes?

Yes, FDA may use an official sample, including the 702(b) portion, for research purposes, provided that the conditions for destruction under 21 CFR 2.10(e) are met. In such situations, because FDA has met the conditions for destruction, the owner is no longer entitled to the 702(b) portion of the sample.

10. How should the owner request a 702(b) portion?

The owner should send a request for the 702(b) portion of an official sample to the FDA Division[4] of the officer or employee who collected the sample. The request can be addressed to the Division's Director of Compliance.[5] The request for a 702(b) portion must be in writing (e.g., electronic mail or letter) and be accompanied by either a showing of ownership of the sample or the authority to receive the sample on behalf of the owner (21 CFR 2.10(c)). The request should also include relevant details regarding the sample (e.g., the lot, serial number, model number, or other identification of the sampled product). The owner who requests the 702(b) portion must specify the amount desired. (21 CFR 2.10(c)(2)). In addition to the request,

[4] FDA's Office of Regulatory Affairs (ORA) staff are assigned to program areas, where they specialize in a commodity. Each program area is organized by Divisions. See https://www.fda.gov/about-fda/office-regulatory-affairs/ora-program-division-boundary-maps-and-fact-sheets for more information.
[5] Contact information is available at https://www.fda.gov/about-fda/contact-ora/ora-field-leadership-contacts.

the owner should, if available, provide a copy of the Form FDA 484 Receipt for Samples issued by the collecting officer or employee to the responsible individual from whom the sample was collected to facilitate FDA's identification of the sample that was collected (see IOM, Chapter 4 for a copy of Form FDA 484).

In responding to the request, the FDA Division for the officer or employee who collected the sample may consult, as needed, with ORA's Office of Regulatory Science, FDA's Office of Chief Counsel, the appropriate FDA Center, the laboratory holding the 702(b) portion, as well as the Division in which the officer or employee is located, if different from the Division that collected the sample.

CERTIFICATES OF CONFIDENTIALITY

Guidance for Sponsors, Sponsor-Investigators, Researchers, Industry, and Food and Drug Administration Staff

Comments may be submitted at any time for Agency consideration. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Policy
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Devices and Radiological Health
Center for Tobacco Products
Center for Food Safety and Applied Nutrition
Center for Veterinary Medicine
Office of Chief Scientist

September 2020

Contains Nonbinding Recommendations

CERTIFICATES OF CONFIDENTIALITY

Guidance for Sponsors, Sponsor-Investigators, Researchers, Industry, and Food and Drug Administration Staff

Additional copies are available from:
Office of Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 32., Rm. 4239
Silver Spring, MD 20993-0002
Phone: 301-796-4850 or at
https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration

September 2020

Table of Contents

CERTIFICATES OF CONFIDENTIALITY

Guidance for Sponsors, Sponsor-Investigators, Researchers, Industry, and Food and Drug Administration Staff

I. Introduction

This guidance[1] describes FDA implementation of the revised provisions applicable to the request for, and issuance of, a Certificate of Confidentiality (CoC). The 21st Century Cures Act (Cures Act) (Public Law 114-255) amended the Public Health Service Act (PHS Act), section 301(d) (42 U.S.C. 241(d)) relating to the issuance of CoCs. A CoC is intended to help protect the privacy of human subject research participants from whom identifiable, sensitive information is being collected or used in furtherance of the research.[2] Historically, a CoC generally protected a researcher from being compelled to disclose identifiable, sensitive information about the research participant, created or compiled for purposes of the human subject research. As amended, the statute broadened the protections by affirmatively prohibiting holders of CoCs from disclosing such information unless a specific exception applies.

The Cures Act simplified certain aspects of the issuance of CoCs by requiring that CoCs be issued for federally-funded human subject research that collects or uses identifiable, sensitive information (referred to in this guidance as mandatory CoCs). For non-federally funded research, issuance of CoCs is not required but may be issued at the discretion of FDA (referred to in this guidance as discretionary CoCs). FDA intends to continue receiving and considering such requests and will issue discretionary CoCs as appropriate. This guidance is intended to provide information on how to request a *discretionary* CoC, the statutory requirements for requesting such a CoC, and the statutory responsibilities associated with possessing a CoC. Although the mandatory CoC and the discretionary CoC are issued under different processes, the protections

[1] This guidance has been prepared by the Office of Policy in cooperation with the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, the Center for Tobacco Products, the Center for Food Safety and Applied Nutrition, the Center for Veterinary Medicine, and the Office of Chief Scientist at the Food and Drug Administration.

[2] There are additional statutes and regulations that protect the privacy of human subject research participants. These are outside the scope of this guidance.

afforded by the issuance of either CoC are identical and the statutory responsibilities are the same.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

A CoC generally protects a researcher from being compelled to disclose identifiable, sensitive information about the research participant, created or compiled for purposes of the research, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding. As amended, the statute broadened these protections by prohibiting disclosure of such information. By protecting researchers from being compelled to disclose identifiable, sensitive information about the research participants, CoCs help protect the identity of the research participants and achieve the objectives of the research. There are exceptions to the prohibition on disclosure as described in Section III of this guidance.

FDA has the authority (by delegation) to issue CoCs related to the study of products subject to FDA jurisdiction and to which FDA regulations apply, in compliance with the PHS Act, and has done so for over 20 years. (42 U.S.C. § 241)[3] The Cures Act revisions made issuance of a CoC mandatory for federally funded researchers "engaged in biomedical, behavioral, clinical, or other research, in which identifiable, sensitive information is collected (including research on mental health and research on the use and effect of alcohol and other psychoactive drugs)." For *non-federally funded research*, FDA "*may*, upon application by a person engaged in research, issue to such person a certificate of confidentiality to protect the privacy of such individuals (emphases added) . . . ."

The Cures Act also directed agencies to take steps to minimize the burden to researchers, streamline the process, and reduce the time it takes to comply with the requirements of the statutory provision. FDA has complied with this directive in implementing requirements for the issuance of mandatory CoCs to FDA-federally funded researchers.

For non-federally funded research, FDA has been issuing discretionary CoCs pursuant to the amended statutory requirements, on a case-by-case basis upon application to FDA, since enactment of the Cures Act. This guidance describes the revised, streamlined process for submission to FDA of requests for discretionary CoCs for non-federally funded research. The revised process for discretionary CoCs will minimize the burden to researchers who request a CoC, will streamline the existing process by reducing the information currently provided in a request to FDA for a CoC, will clarify the statutory responsibilities associated with receiving a CoC and, thus, will reduce the time it takes to obtain a CoC.

[3] FDA, by delegation from the Secretary, Department of Health and Human Services (HHS), has the authority to issue CoCs . (See, FDA Staff Manual Guide, 1410.26(1)(E)). Other HHS agencies, e.g., National Institutes of Health (NIH), Centers for Disease Control and Prevention, also issue CoCs.

III. Scope

To help ensure that discretionary CoCs are issued to those entities who can comply with the requirements of the statutory provision, we recommend that only sponsors or sponsor-investigators, submit requests for discretionary CoCs (as defined in 21 CFR §50.3, §312.3, §812.3) (i.e., the individual who takes responsibility for or initiates the clinical investigation). This will help eliminate duplicative requests to FDA for the same human subject research. It is our understanding that, typically, sponsors and sponsor-investigators are the entities or individuals who have responsibility and control over the information and data collected and used in research. Furthermore, the human subject research, for which a discretionary CoC is being requested, must involve the use or study of a product subject to FDA's jurisdiction and must be subject to FDA's regulatory authority.

The term "identifiable, sensitive information," as used in section 301(d), PHS Act, and in relation to CoCs, means "information that is about an individual and that is gathered or used during the course of research" covered by the statute and

> (A) through which an individual is identified; or (B) for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

(42 U.S.C. § 241(d)(4)). An entity or individual requesting a discretionary CoC should evaluate its own human subject research and make its own determination as to whether the research involves the collection of identifiable, sensitive information (e.g., research participant names). This evaluation should take into account the type of information collected, whether the information is retained for any further use or purpose, the extent of the information, and the security of the data systems that contain the information. In considering whether the individual information being collected is "identifiable, sensitive information," sponsors, sponsor-investigators, and other researchers should be aware of the evolving perspectives as to the identifiability of the information collected. Given current technological capabilities, there is some support for the position that the identity of an individual participating in certain types of research is relatively easy to determine even with limited de-identified data. Genomic data also are often considered to fall automatically into the category of identifiable, sensitive information.[4] There are various definitions of the phrase identifiable, sensitive information used by different government agencies and for different purposes – not all necessarily applicable in this context but which may be useful in an evaluation by the sponsors, sponsor-investigators, and other researchers of whether certain information would fall within the statutory definition.[5] A

[4] NIH considers research in which identifiable, sensitive information is collected or used, to include "research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained." (NIH, NOT-OD-17-109: Notice of Changes to NIH Policy for Issuing Certificates of Confidentiality, effective October 1, 2017).

[5] Department of Health and Human Services, Office of the Chief Information Officer. (2016). The Department of Health and Human Services Cybersecurity Awareness Training, FISCAL YEAR 2016. Retrieved February 26, 2020, from https://www.hhs.gov/sites/default/files/ocio/securityprivacy/awarenesstraining/cybersecurity-awareness.pdf.

determination of whether any data or information collected during human subject research is identifiable, sensitive information should be made by the sponsors or sponsor investigators.

Once a CoC is issued, the recipient must comply with the statutory disclosure protections as follows (section 301(d)(1), PHS Act):

> (A) [*defines who can apply and conditions of applying for a CoC*].
> (B) Except as provided in subparagraph (C), any person to whom a certificate is issued . . . to protect the privacy of individuals described in such subparagraph shall not disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.
> (C) The disclosure prohibition in subparagraph (B) shall not apply to disclosure or use that is—
>
> > (i) required by Federal, State, or local laws, excluding instances described in subparagraph (D); (ii) necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual; (iii) made with the consent of the individual to whom the information, document, or biospecimen pertains; or (iv) made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.
>
> (D) Any person to whom a certificate is issued . . . to protect the privacy of an individual described in such subparagraph shall not, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, disclose or provide the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, except in the circumstance described in subparagraph (C)(iii).
> (E) Identifiable, sensitive information . . ., and all copies thereof, shall be immune from the legal process, and shall not, without the consent of the individual to whom the information pertains, be admissible as evidence or used for any purpose in any action, suit, or other judicial, legislative, or administrative proceeding.
> (F) Identifiable, sensitive information collected by a person to whom a certificate has been issued . . ., and all copies thereof, shall be subject to the protections afforded by this section for perpetuity.
> (G) The Secretary shall take steps to minimize the burden to researchers, streamline the process, and reduce the time it takes to comply with the requirements of this subsection.

As part of the protection of the identifiable, sensitive information collected in the research, any other entities with whom the sponsor, sponsor-investigator, or other researcher shares the information (i.e., "copies" of the information) are also subject to the disclosure requirements. Such entities include contract research organizations, clinical investigators, and academic institutions, among others.

Under FDA regulations, an Institutional Review Board (IRB) is a group that has been formally designated by an institution to review, approve the initiation of, and conduct periodic review of

biomedical research involving human subjects. (21 CFR §56.102(g)). In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove such research. (21 CFR §56.109(a)). An IRB review serves an important role in the protection of the rights and welfare of human research subjects. If an IRB in reviewing research determines that particular data collected in a clinical trial are sufficiently sensitive to warrant requesting a CoC, then it is within the purview of an IRB to request that a CoC be obtained in order to secure IRB approval. Any disagreement between an IRB, sponsor, and/or clinical investigators, regarding the need to request a CoC for a particular study should be resolved by appropriate communications among those parties.

IV. Request for Discretionary CoC From FDA

Prior to submitting a request to FDA for issuance of a discretionary CoC, the potential requestor should consider the following questions:

- Is the requestor involved in human subject research in which identifiable, sensitive information is collected?
- Is the requestor a sponsor or sponsor-investigator or authorized representative (i.e., the individual who takes responsibility for or initiates the clinical investigation)?
- Does the human subject research, for which a discretionary CoC is being requested, involve the use or study of a product subject to FDA's jurisdiction and subject to FDA's regulatory authority?
- Are the requestor's research measures sufficient to protect the confidentiality of the identifiable, sensitive information? [6]

We recommend that a request to FDA for the issuance of a discretionary CoC be made by those entities and individuals that can answer "yes" to all of these questions. A request for a discretionary CoC also should not be made if the human subject research is federally funded.[7] We also prefer that all requests for discretionary CoCs be submitted electronically as described in this section and with the information and assurances as detailed in this section.

To make a request to FDA for a discretionary CoC, the requestor should determine the appropriate Center and submit the request, in the form of a letter (e.g., as a PDF attachment to the email submission), through one of the following email addresses:

Center for Drug Evaluation and Research (CDER) at: CDER-CoC-Requests@fda.hhs.gov
Center for Biologics Evaluation and Research (CBER) at: CBERBIMONotification@fda.hhs.gov
Center for Devices and Radiological Health (CDRH) at: CDRH-CoC@fda.hhs.gov
Center for Tobacco Products (CTP) at: CTP_RIHSC@fda.hhs.gov

[6] The amendments to section 301(d) of the PHS Act, signal Congressional support for enhanced privacy protections for participants in research. FDA recommends that sponsors and investigators explore ways to further enhance their own privacy and confidentiality procedures.

[7] As noted in Section II, CoCs for federally funded research are mandatory and outside the scope of this guidance. Mandatory CoCs for federally funded research are handled in a different manner than discretionary CoCs.

Center for Food Safety and Applied Nutrition (CFSAN) at: CFSAN-CoC-Requests@fda.hhs.gov
Center for Veterinary Medicine (CVM) at: AskCVM@fda.hhs.gov

We recommend the request letter include the following information and assurances to facilitate FDA's review and to expedite consideration of the request for the discretionary CoC.

Descriptive Information

- Sponsor or Sponsor-Investigator Name or authorized representative (e.g., the individual who takes responsibility for or initiates the clinical investigation).
- Sponsor or Sponsor-Investigator or authorized representative Address (same as on file with FDA).
- Sponsor or Sponsor-Investigator or authorized representative Email Address.
- FDA Application Number, as applicable, (e.g., IND/NDA/BLA/IDE/HDE/PMA/PMTA/ITP)[8].
- ClinicalTrials.gov Numerical Identifier (if applicable) (number provided upon registration on www.ClinicalTrials.gov).
- Research Title
- If conducting human subject research subject to FDA's jurisdiction but the sponsor or sponsor-investigator is exempt from submission of an investigational application (e.g., IND/IDE) submit all of the above information with the exception of the FDA application number.
- Signature of sponsor, sponsor-investigator, or authorized representative, submitting the discretionary CoC request.

Assurances

The requestor should include information sufficient to allow FDA to assess whether the requestor understands its obligations to comply with the CoC statutory provisions (section 301(d), PHS Act, (42 U.S.C. 241(d))). We recommend use of the following language in the request letter to facilitate FDA's review:

> *The requestor is engaged in biomedical, behavioral, clinical, or other research, in which identifiable, sensitive information is collected or used.*
>
> *The requestor agrees it is responsible for complying with requirements to protect the confidentiality of identifiable, sensitive information that is collected or used in biomedical, behavioral, clinical, or other research.*
>
> *The requestor agrees not to disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive*

[8] Investigational New Drug Application/New Drug Application/Biologics License Application/Investigational Device Exemption/Humanitarian Device Exemption/Premarket Application/Premarket Tobacco Product Application/Investigational Tobacco Product.

information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains. The requestor also agrees not to disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.

The requestor understands that the identifiable, sensitive information collected by a researcher to whom a discretionary CoC has been issued, and all copies of such information, are subject to the protections afforded by the statute in perpetuity.
The requestor understands and agrees that disclosure is permitted by the recipient of a CoC only when:

- *Required by Federal, State, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding;*
- *Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;*
- *Made with the consent of the individual to whom the information, document, or biospecimen pertains; or*
- *Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.*

The requestor also should note that the signature provided for this request, if a facsimile or e-signature, represents a true and correct signature of the sponsor, sponsor-investigator, or that of an authorized representative, authorized to submit this request for a Certificate of Confidentiality and to make these assurances.

V. FDA Review and FDA Issuance of Discretionary CoC

After a request has been sent to the appropriate Center responsible for the FDA-regulated product, a review will be conducted to ensure the requestor has submitted all the information and assurances, described in Section IV. After FDA completes its review, the Center will send an electronic response letter to the requestor indicating whether or not the discretionary CoC has been granted. If granted, that electronic response letter will serve as the CoC. It is expected that most discretionary requests will be granted provided these are in compliance with the statutory requirements. The recipient of the CoC is expected to carry out the statutory assurances provided in the request and reiterated in the FDA electronic response letter for the protection of the individuals participating in the human subject research.