

***Providing Regulatory Submissions in Electronic and  
Non-Electronic Format—Promotional Labeling and  
Advertising Materials for Human Prescription Drugs  
Draft Guidance for Industry***

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# Outline

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- Content, Format and Tips for submissions
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# Background

# Legal Overview

- Section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), added by Section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA)
  - Requires that certain submissions must be submitted in electronic format specified by FDA, beginning no earlier than 24 months after FDA issues a final guidance specifying such electronic submission format

# Promotional Materials under Section 745A(a)

- Draft Guidance proposes two types of promotional material-related submissions are subject to the requirements of section 745A(a)
  - Promotional materials submitted in fulfillment of the postmarketing reporting requirements (i.e., Form FDA 2253 submissions or “2253 submissions”)
  - Presubmissions of promotional materials for accelerated approval products and for products approved when human efficacy studies are not ethical or feasible

# Timeline

- 24 months after the issuance of *this* guidance in *final* form, firms will be **required** to submit all promotional submissions that fall within section 745A(a) electronically (e.g., in eCTD format)
- Draft Guidance notes that firms are not required—but are **STRONGLY** encouraged to—submit electronically other types of promotional material submissions
  - NOTE: Complaints should only be submitted as **paper copies** and cannot be accepted in eCTD



# Overview of the Draft Guidance

# Purpose

- Outlines proposed requirements and recommendations for firms on how to make submissions pertaining to promotional materials for human prescription drugs to FDA.
- Describes specific aspects of submitting promotional materials using module 1 (M1) of the electronic Common Technical Document (eCTD) using version 3.3 or higher of the *us-regional-backbone file*
  - OPDP can only accept submission of promotional materials using version 3.3 or higher of the us-regional-backbone file



# Scope

## **Submissions pursuant to section 745A(a) of the FD&C Act**

- 2253 submissions
- Presubmissions of promotional materials for accelerated approval products and for products approved when human efficacy studies are not ethical or feasible

## **Other promotional material-related submissions**

- Voluntary advisory submissions
- 503C TV ads
- Resubmissions
- General correspondences
- Amendments
- Withdrawal requests
- Responses to notice of violation or warning letter
- Responses to information request
- Reference documents
- Complaints

# Binding Requirements vs. Nonbinding Recommendations

- Binding
  - portions of this draft guidance regarding requirements for electronic submissions pursuant to section 745A(a) of the FD&C Act will have binding effect 24 months after FDA issues a final guidance
- Nonbinding
  - all other proposals are suggestions and recommendations for electronic submissions of promotional-related materials



# Content, Format & Tips for Submissions

# General Considerations

- Draft Guidance proposes all promotional submissions should:
  - Include appropriate NDA, ANDA, or BLA number(s)
  - Submit different types of promotional material submissions separately (e.g., do not combine a postmarketing 2253 and request for advisory submission)
  - Submit promotional submissions separately from other types of submissions not related to promotion
  - Submit promotional materials directed to HCPs separately from those directed to consumers
  - Use Form FDA 2253 appropriately for OPDP vs. APLB
  - NOT include Form 356h

# 2253 Submissions

- Firms are currently required to submit specimens of promotional materials for a prescription drug product at the time of initial dissemination or publication
- Required items for 2253 submissions:
  - Completed Form FDA 2253
  - Promotional materials
  - Current product labeling

# Location within US-Regional- Backbone File for 2253 Submissions

- **Form FDA 2253- Section 1.1**
  - When submitting to multiple applications, the Draft Guidance provides instruction to note the lead application on the Form FDA 2253 and include an attachment listing the other application numbers
  - Attachment containing any additional application numbers should be submitted in section 1.1 with the Form FDA 2253
  - Only 1 application type (e.g. NDA or BLA) per submission

# Location within US-Regional-Backbone File for 2253 Submissions (cont'd)

- **Current Product Labeling- Section 1.14.6**
  - Firms are required by regulation to submit the most current labeling
  - May include either a file or a reference link to a previously submitted copy of the current product labeling
  - If a reference link is used, it must reference the current product labeling at time of submission

# Location within US-Regional-Backbone File for 2253 Submissions (cont'd)

- **Promotional Materials- Section 1.15**
  - Draft Guidance proposes that Professional and Consumer materials should be submitted separately
  - Promotional Material Audience Type should match the Audience Type on the corresponding Form 2253
  - Do NOT include any files under Section 1.15.1 Headings when submitting Form 2253
  - Materials should be included under Section 1.15.2
  - Material Attributes include promotional material type, material id, and issue date



# Location within US-Regional-Backbone File for 2253 Submissions (cont'd)

- **Promotional Materials- Section 1.15 (cont'd)**
  - Do not submit duplicate material IDs under the same 2253 submission
  - Issue Date format is YYYYMMDD
  - Clean copy of materials submitted under Heading **1.15.2.1.1**
  - Annotated copy of materials may be submitted under **1.15.2.1.2**
  - Annotated labeling may be submitted under **1.15.2.1.3**
  - Do NOT submit current product labeling under **1.15.2.1.3**
  - Annotated references may be submitted under **1.15.2.1.4**

# Amendment to 2253 Submission

- Draft Guidance proposes if a previous 2253 submission is missing one or more of the promotional materials listed on the Form FDA 2253, these materials should be submitted as Amendments
- Only submit an Amendment if missing materials have not been requested by FDA

# Location within US-Regional-Backbone File for Amendment to 2253 Submission

- Draft Guidance proposes that amendments should include the following:
  - Correspondence stating that it is an amendment that includes accompanying promotional materials that were previously missing or rejected (refer to section VI.E of the draft guidance for details on content of the correspondence)- **Section 1.15.1.8**
  - Promotional materials that were missing from previous submission; the firm does not need to resubmit the entire 2253 submission- **Section 1.15.2**
  - Same guidelines as 2253 submission above

# 2253 Submissions: Reference Documents

- Draft Guidance proposes that reference documents are annotated references or annotated promotional materials that were missing from a previous submission to FDA
- NOT mandatory for 2253 submissions
- Do NOT submit promotional materials that were entirely omitted from a previous submission as Reference Documents (these should be submitted as Amendments)

# 2253 Submissions: Reference Documents (cont'd)

- Reference documents should include the following:
  - Correspondence stating that it is a reference document submission and the specific information regarding what is in the submission (i.e., annotated references, annotated promotional materials, and/or annotated labeling) (refer to section VI.E of the draft guidance for details on content of correspondence.)
  - Annotated references, annotated promotional materials, and/or annotated labeling



# Location within US-Regional-Backbone File for Reference Documents for 2253 Submissions

- Correspondence- **Section 1.15.1.10 Submission of Annotated References**
- Annotated materials that were missing from previous submission- **Section 1.15.2 Materials**
  - Heading 1.15.2.1.1 – Clean Version may be left empty
  - Annotated Version- 1.15.2.1.2
  - Annotated Labeling version- 1.15.2.1.3
  - Annotated References- 1.15.2.1.4



# Draft Guidance Tips for FDA Form 2253 Submissions

- Annotated versions of the promotional material(s), annotated labeling, and references are helpful to FDA, but optional. Only the clean version of the material in section 1.15.2.1.1 is required.
- May submit the current product labeling with each 2253 submission. Alternatively, once product labeling is submitted to section 1.14.6 with a 2253 submission, may cross reference the current product labeling within the XML backbone.
- If firms choose to reference the current product labeling within the XML backbone, ensure that the version of the product labeling that is referenced is correct and that the leaf title is revised with each 2253 submission to be informative for Agency reviewers (e.g., include the date of submission).

# Draft Guidance Tips for FDA Form 2253

## Submissions (cont'd)

- Websites: In general, firms must submit entire website at time of first use. If one page or section of website is updated, only need to submit the updated page or section with a cross-reference to the original submission of the website noted in Comments section of Form FDA 2253, including the date of original submission. If website is substantially revised, submit the revised website in its entirety.
- Do NOT submit any correspondence in section 1.15.1 or 1.2
- Do NOT include a 356h form
- For drugs with multiple approved indications, when possible submit promotional materials that only promote one indication separately from promotional materials that promote only another indication



# Non-2253 Submissions in eCTD

- **Section 1.15.1.1 through Section 1.15.1.11**
  - Select appropriate heading based on the type of submission
  - Submit correspondence file to the appropriate heading
  - Reminder: Please do NOT submit promotion-related correspondence in Section 1.2
  - Correspondence heading selected must comport with material doc type attribute in section 1.15.2 (e.g. if “1.15.1.1 Request for advisory comments on launch materials” selected, Section 1.15.2 should be “Request for Advisory Launch”)

# Non-2253 Submissions in eCTD

## (cont'd)

- If the submission contains promotional materials –
  - **Section 1.15.2 Materials:** Include attribute for promotional-material-doc-type
    - **1.15.2.1 Material:** Include attribute for promotional-material-type and material-id (do NOT use issue-date attribute)
    - **1.15.2.1.1 Clean version:** Promotional piece
    - **1.15.2.1.2 Annotated version:** Annotated promotional piece (e.g., annotated storyboard for TV ads, annotated patient brochure)
    - **1.15.2.1.3 Annotated labeling version:** Annotated approved product labeling (PI, PPI, Medication Guide)
    - **1.15.2.1.4 Annotated references:** Annotated references for product claims and disease/epidemiology claims, spokesperson verification

# Request for Advisory Comments

- Sponsors may voluntarily submit promotional materials for advisory comments to FDA prior to publication (21 CFR 202.1(j)(4))
  - **Launch:** Draft promotional materials that are voluntarily submitted by a firm to FDA during the launch phase (i.e., the first 120 days that an FDA-approved product, indication, delivery system, formulation, dosage form, dosing regimen, strength, or route of administration is marketed to the public) for review and comment prior to dissemination or publication.
  - **Non-launch:** Refers to draft promotional materials that are voluntarily submitted after the launch phase (i.e., after the first 120 days as described above) for review and comment prior to first use in the public domain.

# Request for Advisory Comments (cont'd)

Draft Guidance proposes that the submission should contain:

- Correspondence letter
  - Subject line should include “Request for Advisory Comments on [Launch or Non-Launch] Materials”
  - Designate “launch” or “non-launch”
  - Identify each promotional piece being submitted
  - Include the material ID, if available, and the type of material
  - Designate “core” or “non-core” pieces
  
- Clean version of the draft promotional material(s)
  
- Annotated copy of the proposed promotional material that clearly identifies the source of support for each claim



# Request for Advisory Comments (cont'd)

- Most current FDA-approved PI and, if applicable, the FDA-approved patient labeling or Med Guide, with annotations cross-referenced to the proposed promotional material
- If applicable, annotated references to support product claims not contained in the PI, cross-referenced to the proposed promotional material
- If applicable, annotated references to support disease or epidemiology information, cross-referenced to the proposed promotional material
- **For OPDP:** For draft promotional materials, do NOT include Form FDA 2253 with the submission

# Amendments vs. Reference Documents for Advisory submissions

- Draft Guidance proposes sponsors submit an **Amendment** when:
  - a request for advisory comments is missing one or more of the promotional materials listed in the correspondence
  - **Example:** A firm submits a request for advisory comments using eCTD. The correspondence file states that three promotional materials are included in the submission along with annotated copies and references. However, upon receipt, FDA notes that the actual submission only includes two promotional materials with annotated copies and references. The firm should submit the missing promotional material and the annotated copy and references as an amendment using eCTD. The subject line of the correspondence should note that the submission is an amendment and include the MA number.

# Amendments vs. Reference Documents for Advisory submissions (cont'd)

- Submit a **Reference Document** when:
  - annotated materials (references, labeling, promotional pieces) were missing from a previous submission
  - **Example:** A firm submits a request for advisory comments that includes two clean copies of promotional materials. However, the submission does not include annotated copies of the promotional materials or annotated references. The firm should submit the missing annotated materials as a reference document. The subject line of the correspondence should note that it is a reference document submission and include the MA number.



# Tips for Requests for Advisory Comments

- Draft Guidance proposes sponsors submit promotional materials directed to HCPs separately from those directed to consumers
- Contact OPDP to confirm receipt if especially time sensitive (e.g., press releases)
- For draft promotional materials, do NOT include Form FDA 2253 with the submission. Do NOT submit anything in section 1.1
- Do NOT submit anything in section 1.2 or 1.14.6
- Do NOT use the Issue-date attribute in section 1.15.2.1 (use for 2253 submissions only)



# Tips for Requests for Advisory Comments (cont'd)

- Annotated references may not be necessary in section 1.15.2.1.4 (depending on the material and claims)
- If literature references are already used in Modules 3, 4, or 5, should resubmit with proper annotations for specific promotional material
- Resubmissions: Some companies choose to submit a revised version of the draft promotional material for advisory comment
  - Use the *submission-sub-type* of *resubmission*
  - Use the “replace” operator attribute to replace the previously submitted files with the resubmission’s updated files.

# Presubmissions for Accelerated Approval Products

- Presubmission of promotional materials pursuant to 21 CFR 314.550 (subpart H) or 21 CFR 601.45 (subpart E)
  - During the preapproval review period, applicants must submit to the Agency all promotional materials intended for dissemination or publication within 120 days following marketing approval (launch)
  - After 120 days following marketing approval, unless otherwise informed by the Agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination or publication of the promotional material (non-launch)



# Presubmissions for Accelerated Approval Products (cont'd)

The submission should contain:

- Correspondence Letter
  - Subject line should indicate that this is a presubmission under 21 CFR 314.550 or 21 CFR 601.45
  - Designate “launch” or “non-launch”
  - Identify each promotional piece being submitted
  - Include the material ID, if available, and the type of material
  - Designate “core” or “non-core” pieces
  - Prioritize list of promotional materials for review
- Similar eCTD submission structure as Request for Advisory
- **Section 1.15.1.3** Presubmission of launch promotional materials for accelerated approval products  
OR  
**Section 1.15.1.4:** Presubmission of non-launch promotional materials for accelerated approval products



# Important Considerations

# Presentation Issues – Unique Challenges with Promotional Materials

- Draft Guidance proposes that optimally, Agency reviewers should be able to use or view each promotional piece submitted to the Agency in the same manner as the end-user audience
- Clear and legible text and images – the majority of images and text within each electronic file should not require excessive magnification in order to obtain the net impression of the piece or an understanding of the individual claims
- Concise description of use – include in Comments section of 2253 form or in correspondence for non-2253s, especially important when the purpose of the piece is not self-evident after looking at an image or reading its title
- Layout indicators – examples include page numbers, indicators of tabs or section dividers, pockets and pocket content, etc.
- Websites, electronic interactive programs, electronic detail aids, etc. – should clearly display and communicate how the promotional piece will look and convey messages to the end user. Submission may be accompanied by a video showing manipulation of the promotional program or application.

# Presentation Issues – Unique Challenges with Promotional Materials (cont'd)

- Materials requiring physical manipulation by the end user in order to obtain the net impression or details of the promotional message – submit in a format that allows FDA to view all aspects of the promotional piece (e.g., submit both images for a lenticular magnet that displays one image if tilted left and alternate image if tilted right)
- Three-dimensional objects – electronic submissions should provide sufficient detail to view the promotional material from all possible views; also include point size or dimensions.
- Multi-page spreads – include a clear image or representation of the entire spread within a single view
- Kits – clearly indicate the components of the kit
- Dimensions – include with all images of physical materials



# Collaborative Marketing Agreements

Draft Guidance proposes that in cases where a company that holds the application collaborates with another firm in order to promote the drug, the application holder should send a general correspondence to OPDP describing the agreement.

- Subsequent submissions of promotional materials should also indicate the business relationship (e.g., Comments section on 2253 form, cover letter, etc.)
- For eCTD submissions, both companies should be using the same version of the *us-regional-backbone* file
- Both companies should work together to come up with a system for generating sequence numbers in order to avoid the use of duplicate sequence numbers (e.g., assign a block of numbers to a particular vendor)

# Grouped Submissions

- Additional Applications function allows Sponsors to submit a single eCTD file for multiple Applications
- Functionality is often confused with Application References
- The Lead Application should be listed first in the Additional Applications section
  - Application Containing Files element should = Yes
- Each Grouped Submission can only contain a single Application Type (NDA, ANDA, BLA, IND)
- When submitting a 2253 with Additional Applications, the current promotional labeling for each Application must be included in Section 1.14.6.





# Contact Information

# OPDP Contact Information

- Building 51 on White Oak Campus
  - Suites 3200 & 3300
- Fax numbers
  - 301-847-8444 or 301-847-8445
- Telephone number
  - 301-796-1200
- To begin the process of submitting a sample, email the Electronic Submission Support Team at [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)
- Email address for questions regarding the draft guidance or eCTD submissions to OPDP
  - [OPDPeCTD@fda.hhs.gov](mailto:OPDPeCTD@fda.hhs.gov)
- Email address for general submission questions for OPDP
  - [CDER-OPDP-RPM@fda.hhs.gov](mailto:CDER-OPDP-RPM@fda.hhs.gov)
- Submission address
  - Food and Drug Administration
  - Center for Drug Evaluation and Research
  - 5901-B Ammendale Road
  - Beltsville, MD 20705-1266