


FDA Update: Submission of Promotional Materials

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Presentation Outline

- ▶ Background
- ▶ Timeline for Promotional Submissions in eCTD
- ▶ General Considerations for Submissions
- ▶ Content and Format for Submissions
- ▶ Presentation Issues

Background – Challenges

Challenges with Module 1 – eCTD

- ▶ Insufficient headings and hierarchy
 - Section 1.15 Promotional Material
- ▶ Inconsistent placement of the accompanying PI
 - Section 1.14 Labeling vs. Section 1.15 Promotional Material
- ▶ Lack of naming standards for leaf titles
 - Promotional Piece
 - “Sales Aid 65NO3582 20150102” vs. “promotional piece”
 - FDA Form 2253
 - “FDA Form 2253 Consumer print ad 20150223” vs. “2253 Form”
- ▶ Navigation difficulties

Background – Progress

Progress with Module 1 – eCTD

- ▶ Module 1 has been updated
 - Includes more granularity
 - Utilizes attributes (e.g. audience type, material doc type, material type, material id, and issue date)
 - Allows for identification of characteristics such as:
 - Professional vs. consumer audience
 - Type of submission (e.g. advisory, 2253, accelerated approval presubmission)
 - Type of piece (e.g. TV ad, print ad, sales aid)
- ▶ Draft Guidance, *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*, issued April 21, 2015

Draft Guidance

- ▶ Explains how manufacturers, packers, and distributors (firms) that may either be the applicant or acting on behalf of the applicant, should make submissions pertaining to promotional materials for human prescription drugs and biologic products (“drugs”) to the FDA
- ▶ Pertains to submissions made to CDER (OPDP) and CBER (APLB)

Draft Guidance (cont'd)

- ▶ Applies to human prescription drugs, including biological products that are defined as drugs. Does NOT apply to devices that CBER regulates as biological products.
- ▶ Describes the various types of submissions of promotional materials and general considerations for submissions submitted in paper or electronic format
- ▶ Describes specific aspects of submission of promotional materials using module 1 of eCTD using version 3.3 or higher of the *us-regional-backbone file*

Section 745A(a) of the FD&C Act

- ▶ 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 submissions under section 505(b), (i), or (j) of the FD&C Act, and submissions under section 351(a) or (k) of the Public Health Service Act (PHS Act), 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)

Two types of promotional material-related submissions are considered 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”)
- ▶ Presubmission of promotional materials for accelerated approval products

Timeline

- ▶ Therefore, 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)
- ▶ Firms may—and are strongly encouraged to—submit electronically other types of promotional material submissions

Collaborative Marketing Agreements

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/APLB 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)

Types of Promotional Submissions

- ▶ Promotional materials submitted in fulfillment of the postmarketing reporting requirements (2253 submissions)
- ▶ Presubmission for accelerated approval products
 - Launch
 - Non-launch
- ▶ Request for advisory
 - Launch
 - Non-launch
- ▶ 503C TV ad submission (Pre-dissemination of TV ads: Guidance is draft, not for implementation at this time)
- ▶ Resubmission
- ▶ General Correspondence
- ▶ Amendment
- ▶ Withdrawal Request
- ▶ Response to Untitled or Warning Letter
- ▶ Response to Information Request
- ▶ Reference Documents
- ▶ Complaint (Not accepted in eCTD - hard copy only)

General Considerations

All promotional submissions should:

- ▶ Include appropriate NDA, ANDA, or BLA number(s)
- ▶ Use the most specific material type (from Form FDA 2253)
- ▶ Submit different types of promotional material submissions separately (e.g. do not combine together 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
- ▶ NOT include promotion-related correspondence in Section 1.2 in eCTD
- ▶ Use informative leaf titles in eCTD (ok if redundancy with attributes for 1.15.2.1 which capture material type, ID, and issue date)

1.15 Promotional Material Section

1.15 Promotional material [promotional-material-audience-type]

1.15.1 Correspondence relating to promotional materials

1.15.1.1 Request for advisory comments on launch materials

1.15.1.2 Request for advisory comments on non-launch materials

1.15.1.3 Presubmission of launch promotional materials for accelerated approval products

1.15.1.4 Presubmission of non-launch promotional materials for accelerated approval products

1.15.1.5 Pre-dissemination review of television ads

1.15.1.6 Response to untitled letter or warning letter

1.15.1.7 Response to information request

1.15.1.8 Correspondence accompanying materials previously missing or rejected

1.15.1.9 Withdrawal request

1.15.1.10 Submission of annotated references

1.15.1.11 General correspondence

1.15.2 Materials attribute = [promotional-material-doc-type]

1.15.2.1 Material [promotional-material-type, material-id, issue-date]

1.15.2.1.1 Clean version

1.15.2.1.2 Annotated version

1.15.2.1.3 Annotated labeling version

1.15.2.1.4 Annotated references

Section 1.15

▶ **1.15 *Promotional material [promotional-material-audience-type]***

- Promotional Material Audience Type
 - Consumer
 - Professional
- Reminder: Please do NOT submit consumer directed promotional materials and health care professional directed materials in the same sequence

Section 1.15.1

- ▶ 1.15.1 Correspondence relating to promotional materials
 - **1.15.1.1 Request for advisory comments on launch materials**
 - **1.15.1.2 Request for advisory comments on non-launch materials**
 - **1.15.1.3 Presubmission of launch promotional materials for accelerated approval products**
 - **1.15.1.4 Presubmission of non-launch promotional materials for accelerated approval products**
 - **1.15.1.5 Pre-dissemination review of television ads**
 - **1.15.1.6 Response to untitled letter or warning letter**
 - **1.15.1.7 Response to information request**
 - **1.15.1.8 Correspondence accompanying materials previously missing or rejected**
 - **1.15.1.9 Withdrawal request**
 - **1.15.1.10 Submission of annotated references**
 - **1.15.1.11 General correspondence**
- ▶ Reminder: Please do NOT submit correspondence related to promotional materials in section 1.2
- ▶ Correspondence heading selected in this section must comport with material doc type attribute in section 1.15.2

Section 1.15.2

- ▶ **1.15.2 Materials [promotional-material-doc-type]**
 - Promotional Material Doc Type Attribute describes the type of submission
 - Promotional 2253
 - Request for Advisory Launch
 - Request for Advisory Non-Launch
 - Presubmission Accelerated Launch
 - Presubmission Accelerated Non-launch
 - Pre-Dissemination Review of Television Ads
- ▶ **1.15.2.1 Material [promotional-material-type, material-id, issue-date]**
 - 1.15.2.1.1 Clean version
 - 1.15.2.1.2 Annotated version
 - 1.15.2.1.3 Annotated labeling version
 - 1.15.2.1.4 Annotated references

FDA Form 2253 Submissions

- ▶ The applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. 21 CFR 314.81(b)(3)(i)

FDA Form 2253 Submissions (cont'd)

The submission should contain:

▶ Current Form FDA 2253

- For APLB: Check the “Final” box in Field 14
- For OPDP: Do NOT check the “Draft” or “Final” boxes in Field 14
- Grouped submission: If the promotional material mentions more than one product/application, put lead in Field 3 of the form and include attachment listing other referenced products

▶ Promotional material(s)

▶ Current product labeling

FDA Form 2253 Submissions in eCTD

- ▶ **Section 1.1 Forms:** Include FDA Form 2253 (and attachments if applicable)
- ▶ **Section 1.14.6 Product labeling for 2253 submissions:** Include current product labeling
- ▶ **Section 1.15 Promotional Material:** Include attribute for promotional-material-audience-type
- ▶ **Section 1.15.2 Materials:** Include attribute for promotional-material-doc-type (i.e. Promotional 2253)
- ▶ **Section 1.15.2.1 Material:** Include attribute for promotional-material-type, material-id, and issue date
 - **1.15.2.1.1 Clean version:** Promotional piece
 - **1.15.2.1.2 Annotated version:** Annotated promotional piece (Optional)
 - **1.15.2.1.3 Annotated labeling version:** Annotated approved product labeling (PI, PPI, Medication Guide) (Optional)
 - **1.15.2.1.4 Annotated references:** Annotated references for product claims and disease/epidemiology claims, spokesperson verification (Optional)

Example of an FDA Form 2253 Submission

m1-1-forms

Form FDA 2253: Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use
Form 2253 Consumer Print AD 20120101 [new]

m1-14-6-product-labeling-for-2253-submissions

AXY Sinusitus tablets PI Rev20120101 [new]

m1-15-promotional-material (Consumer)

m1-15-2-materials (Promotional 2253)

m1-15-2-1-material (Print Ad) material-id cpa111 issue-date 20120101

m1-15-2-1-1-clean-version

Consumer Print Ad CPA111 Considerations for treatment of AXY Sinusitus tablets 20120101 [new]

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).

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. (Also see *Guidance for Industry Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics*)
- ▶ 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 Promotional Material:** Include attribute for promotional-material-audience-type
- ▶ **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

- ▶ For those drug products that are not approved under the accelerated approval regulations, 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 (cont'd)

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 (i.e. 2253 code)
 - Designate “core” or “high priority” 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 (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 APLB:** For draft promotional materials, include Form FDA 2253 with line 14 checked as “Draft”
- ▶ **For OPDP:** For draft promotional materials, do NOT include Form FDA 2253 with the submission

Example of Request for Advisory in eCTD

m1-15-promotional-material (Consumer)

m1-15-1-correspondence-relating-to-promotional-materials

m1-15-1-1-request-for-advisory-comments-on-launch-materials

Advisory request - Print Ad New Nasal Spray 20120215 [new]

m1-15-2-materials (Request For Advisory Launch)

m1-15-2-1-material (Print Ad) material-id 98PRTAD

m1-15-2-1-1-clean-version

Launch Ad 98PRTAD New Nasal Spray 20120115 Clean Copy [new]

m1-15-2-1-2-annotated-version

Launch Ad 98PRTAD New Nasal Spray 20120115 ANNOTATED [new]

m1-15-2-1-3-annotated-labeling-version

DRUG XXXX PI Annotated label [new]

Tips for Requests for Advisory

- ▶ Submit promotional materials directed to HCPs separately from those directed to consumers
- ▶ Contact OPDP/APLB to confirm receipt if especially time sensitive (e.g. press releases)
- ▶ OPDP and APLB use the 2253 Form differently:
 - For OPDP: For draft promotional materials, do NOT include Form FDA 2253 with the submission. Do NOT submit anything in section 1.1.
 - For APLB: For draft promotional materials, include Form FDA 2253 in section 1.1 with line 14 checked as “Draft”
- ▶ 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 (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)
 - Applicants must submit to the Agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, 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 of the labeling or initial publication of the advertisement. (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 (i.e. 2253 code)
- Designate “core” or “high priority” pieces
- Prioritize list of promotional materials for review

▶ Similar eCTD submission structure as Request for Advisory

Presubmission for Accelerated Approval Products in eCTD

- ▶ **Section 1.15 Promotional Material:** Include attribute for promotional-material-audience-type
 - ▶ **Section 1.15.1.3 Presubmission of launch promotional materials for accelerated approval products:** correspondence file for a launch accelerated approval presubmission
- OR
- ▶ **Section 1.15.1.4: Presubmission of non-launch promotional materials for accelerated approval products:** correspondence file for a non-launch accelerated approval presubmission
 - ▶ **Section 1.15.2 Materials:** Include attribute for promotional-material-doc-type
 - **1.15.2.1 Material:** Include attribute for promotional-material-type
 - **1.15.2.1.1 Clean version:** Promotional piece
 - **1.15.2.1.2 Annotated version:** Annotated promotional piece
 - **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

Presentation Issues – Unique Challenges with Promotional Materials

- ▶ 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

Future Direction

- ▶ May submit electronic or written comments regarding the draft guidance to the docket
- ▶ Firms are encouraged to submit sample promotional submissions. To begin the process of submitting a sample, email the Electronic Submission Support Team at ESUB@fda.hhs.gov
- ▶ CDER(OPDP) and CBER(APLB) will begin accepting eCTD submissions using M1 Specifications v2.3 in the near future
- ▶ CBER(APLB) will continue to accept eCTD submissions using previous versions of M1 until 24 months after publication of the final version of the promotion guidance

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
- ▶ Email address for questions regarding the draft guidance or eCTD submissions to OPDP
 - OPDPeCTD@fda.hhs.gov
- ▶ Email address for general submission questions for OPDP
 - 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

Ask

