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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 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 (CDER) Marci Kiester at (301) 796-1200; or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-7800.

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)

April 2015
Electronic Submissions

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

Guidance for Industry

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Guidance for Industry[1]

I. INTRODUCTION

This draft guidance pertains to submissions of promotional materials for human prescription drugs (drugs)[2] to the Food and Drug Administration (FDA or the Agency) made by manufacturers, packers, and distributors (firms), whether the applicant or an entity acting on behalf of the applicant. Specifically, this draft guidance pertains to submissions made to the Office of Prescription Drug Promotion (OPDP) in the Center for Drug Evaluation and Research (CDER) and the Advertising and Promotional Labeling Branch (APLB) in the Center for Biologics Evaluation and Research (CBER), and explains certain aspects of electronic submission of promotional materials in module 1 of the electronic Common Technical Document (eCTD) using version 3.3 or higher of the *us-regional-backbone* file.

For the purpose of this draft guidance, the terms *promotional materials* and *promotional pieces* collectively refer to advertising (ads) and promotional labeling materials, regardless of the format, manner, or medium by which they are presented. Promotional materials may include, but are not limited to, television ads, brochures, booklets, detailing pieces, Internet websites, print ads, exhibits, sound recordings, and radio ads.

II. BACKGROUND

A. Electronic Submissions to FDA Under Section 745A(a) of the Federal Food, Drug, and Cosmetic 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) (Pub. L. 112-

[1] This guidance has been prepared by the Office of Prescription Drug Promotion (OPDP) in the Center for Drug Evaluation and Research (CDER) in cooperation with the Advertising and Promotional Labeling Branch (APLB) in the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] The recommendations in this draft guidance apply to biological products that are approved for marketing under section 351 of the Public Health Service Act (PHS Act) and that also meet the definition of "drug" under section 201(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). For such products, the provisions of the FD&C Act applicable to drugs also apply, as well as the regulations implementing these provisions, except that a biological product licensed under section 351 of the PHS Act is not required to have an approved new drug application under section 505 of the FD&C Act (21 U.S.C. 355). See PHS Act section 351(j) (42 U.S.C. 262(j)). Therefore, references to "drugs" in this guidance also include human biological products that fall within the definition. However, this draft guidance does not apply to those devices that CBER regulates as biological products under section 351 of the PHS Act. These submissions are subject to the requirements under section 745A(b) of the FD&C Act. See the final guidance entitled *eCopy Program for Medical Devices Submissions* that implements the electronic copy provisions of section 745A(b) for medical device submissions to FDA. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA webpage at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

144), 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. Certain types of promotional material-related submissions discussed in this guidance are "submissions under subsection (b), (i), or (j) of section 505 of this Act or subsection (a) or (k) of section 351 of the Public Health Service Act," and are, therefore, subject to the requirements of section 745A(a). Specifically, (1) postmarketing submissions of promotional materials using Form FDA 2253 (required by 21 CFR 314.81(b)(3)(i) and 21 CFR 601.12(f)(4)), and (2) submissions of promotional materials for accelerated approval products (required by FD&C Act section 506(c)(2)(B), 21 CFR 314.550 and 21 CFR 601.45) and other products where such submissions are required for approval[3], fall within section 745A(a).

The draft guidance entitled *Providing Regulatory Submissions in Electronic Format—Submissions under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* (745A(a) Implementation Draft Guidance),[4] published in February 2014, sets forth general information on how FDA interprets and intends to implement the electronic submission requirements of section 745A(a) of the FD&C Act. The 745A(a) Implementation Draft Guidance states that it is not feasible to describe and implement the electronic format(s) that would apply to all the submissions covered by section 745A(a) in one guidance document. Instead, FDA will periodically issue guidances specifying the electronic format for certain types of submissions. The revised draft guidance entitled *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (eCTD Revised Draft Guidance) specifies the general format for certain types of electronic submissions using eCTD, including the specifications for module 1.[5]

In addition to the more general information and implementation timeline found in those guidances, this draft guidance provides additional information regarding the format to be used for electronic submission of promotional labeling and advertising materials using eCTD. Accordingly, 24 months after the issuance of this guidance in final form, firms will be required to submit all promotional submissions that fall within the ambit of section 745A(a) electronically as specified in the final guidance. As of that date, paper hard copies will no longer be accepted

[3] In the Federal Register of May 31, 2002 (67 FR 37988), FDA published final regulations (21 CFR 314.640 (Subpart I) and 21 CFR 601.94 (Subpart H)) under which the Agency would allow appropriate studies in animals, in certain cases, to provide substantial evidence of the effectiveness of new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances. This rule applies when adequate and well-controlled clinical studies in humans cannot be ethically conducted and field efficacy studies are not feasible. Sponsors with products approved under these provisions are subject to similar presubmission requirements as accelerated approval products and can use the same procedures outlined in this draft guidance for submitting promotional materials to FDA.

[4] When final, this guidance will represent the FDA's current thinking on this topic.

[5] When final, this guidance will represent the FDA's current thinking on this topic. The current version of the associated technical specification entitled *The eCTD Backbone Files Specification for Module 1* provides additional information. See http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163552.pdf.

for such submissions. Note that while only the promotional submissions that fall within the purview of section 745A(a) will be *required* to be submitted electronically in the format specified in this guidance, firms *may* voluntarily choose to submit electronically other types of promotional material submissions discussed in this guidance. If firms voluntarily opt to submit other types of promotional-related materials electronically, the Agency is currently able to process, review, and archive electronic formats in eCTD and firms are strongly encouraged to make such submissions electronically.

In section 745A(a) of the FD&C Act, Congress granted explicit statutory authorization to FDA to specify in guidance the format for the electronic submissions required under that section. Accordingly, to the extent that this document provides such requirements under section 745A(a), indicated by the use of the words *must* or *required*, this document is not subject to the usual restrictions in FDA's good guidance practice (GGP) regulations, such as the requirement that guidances not establish legally enforceable responsibilities. See 21 CFR 10.115(d).

FDA guidances ordinarily contain standard language explaining that guidances should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. FDA is not including this standard language in this guidance because it is not an accurate description of all of the effects of this guidance. This guidance contains both binding and nonbinding provisions. Insofar as this guidance specifies the format for electronic submissions pursuant to section 745A(a) of the FD&C Act, it will have binding effect.

At the same time, this document also discusses types of promotional materials that are ***not*** subject to the mandatory electronic submission requirement in section 745A, because they are not submissions under section 505(b), (i), or (j) of the FD&C Act or section 351(a) or (k) of the PHS Act (i.e., all promotional materials discussed in this document other than postmarketing submissions of promotional materials using Form FDA 2253 and submissions of promotional materials for accelerated approval products). To the extent that this document includes provisions that do not pertain to the requirements under section 745A(a), this document does not create or confer any rights for or on any person and does not operate to bind FDA or the public, but does represent the Agency's current thinking on this topic. The use of the word *should* in such parts of this guidance means that something is suggested or recommended, but not required. 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.

B. Promotional Labeling and Advertising

Section 201(m) of the FD&C Act defines *labeling* as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article" (21 U.S.C. 321(m)).[6] The U.S. Supreme Court has explained that the language "accompanying such article" in the "labeling" definition is interpreted broadly, to include materials that supplement or explain an article. No physical attachment between the materials

[6] See also 21 CFR 1.3(a).

and the article is necessary; rather, it is the textual relationship between the items that is significant (*Kordel v. United States*, 335 U.S. 345, 350 (1948)).

FDA generally recognizes two types of labeling for drugs: (1) FDA-required labeling and (2) promotional labeling. FDA-required labeling is labeling that is necessary to fulfill the minimum requirements of the FD&C Act and its implementing regulations. For prescription drugs, the required labeling is the labeling, drafted by the manufacturer, that is reviewed and approved by FDA as part of a new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA) (21 CFR 314.50(c)(2), 314.94(a)(8), and 601.2(a)). Promotional labeling is generally any labeling, other than the FDA-required labeling, that is devised for promotion of the product. Examples of materials that may be considered promotional labeling pieces for prescription drugs are described in 21 CFR 202.1(l)(2).

The FD&C Act does not define what constitutes an "advertisement," but FDA regulations provide several examples, including, but not limited to, materials "in published journals, magazines, other periodicals, and newspapers; and advertisements broadcast through media such as radio, television and telephone communication systems" (21 CFR 202.1(l)(1)).

III. GENERAL CONSIDERATIONS

All submissions of promotional materials should meet a set of criteria in order to be reviewed by the Agency. Firms should ensure that the following considerations are met when submitting promotional materials, regardless of the format in which the materials are submitted:

- Include the appropriate NDA, ANDA, or BLA number.

- Use the most specific material type (from Form FDA 2253) to describe the promotional material that is the subject of the submission (e.g., do not use the code "promotional labeling" when another code is available that gives a more specific description of the promotional material).

- Submit different types of promotional material submissions separately (e.g., do not submit materials on Form FDA 2253 pursuant to the requirement in 21 CFR 314.81(b)(3)(i)) together with a request for advisory comments on launch materials).

- Submit ads and promotional labeling separately from other types of submissions (i.e., submissions not related to promotional materials).

- Submit promotional materials directed to healthcare professionals separately from submissions of promotional materials directed to consumers.

Occasionally, promotional materials may be directed both to consumers and healthcare professionals. In those circumstances, firms should identify the audience type based on the end-user for the bulk of the information. For example, press releases should be submitted as consumer-directed materials unless they are specifically intended for healthcare professionals. Websites with distinct sections for healthcare professionals and consumers should be divided

into two separate submissions. If the website does not have distinct sections for each audience and it is not intended to be directed solely to healthcare professionals, firms should submit the entire website as a consumer submission.

In cases where a company that holds the application collaborates with another firm in order to promote the drug (e.g., a collaborative marketing agreement where another firm that is not the application holder disseminates and submits promotional materials based on a contractual agreement with the application holder), the application holder should send a general correspondence submission to OPDP or APLB describing the agreement. In addition, the business relationship should be indicated in subsequent submissions of promotional materials.

IV. CONTENT FOR SPECIFIC TYPES OF SUBMISSIONS[7]

This section describes the content of various types of submissions to the Agency relating to promotional materials. The advertising and promotional labeling submissions described in this section represent the types of submissions that FDA currently receives.

A. Promotional Materials Submitted in Fulfillment of the Postmarketing Reporting Requirements (Form FDA 2253 Submissions)

Under the FD&C Act and FDA's regulations implementing postmarketing reporting requirements, applicants must 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) and 21 CFR 601.12(f)(4)).[8]

This section provides details on submitting promotional materials in fulfillment of postmarketing reporting requirements. OPDP and APLB have different procedures, so firms should pay careful attention to the following information.

Please include the following:

- Form FDA 2253: Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use. (For OPDP submissions, this form should be submitted with ***final*** promotional materials only.) Firms should use the most current version of Form FDA 2253.

- On Form FDA 2253, Box 14 titled "For CBER Products Only:"

[7] Please refer to section VI on how to submit promotional materials in module 1 of the eCTD using *us-regional-v3-3.dtd* or higher. Note that complaints should not be submitted using this process.

[8] For more information, see FDA's January 2014 draft guidance for industry entitled *Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics*. When final, the guidance will represent the FDA's current thinking on this topic.

- OPDP: Do NOT check the "Draft" or "Final" boxes
- APLB: Check the "Final" box only for Final postmarketing submissions

- For cases where promotional materials mention multiple products, please note the lead application number on Form FDA 2253 and include an attachment which identifies the other referenced products (e.g., application type and number, trade name, established name).

- Promotional material(s).

- Current product labeling.

Firms are also encouraged to submit annotated versions of the promotional material(s) cross-referenced to the product labeling and references, if applicable.

Professional and consumer materials should be submitted separately and should not include a cover letter or correspondence. For 2253 submissions to OPDP, if a drug has multiple approved indications that are covered by different reviewers in OPDP,[9] firms should submit (when possible) promotional materials that only promote one indication separately from promotional materials that promote only another indication.

B. Presubmission of Promotional Materials for Accelerated Approval Products

Applicants whose drug products are approved under the accelerated approval framework, FD&C Act section 506(c), 21 CFR 314 (subpart H) and 21 CFR 601 (subpart E), and other products where such submissions are required for approval, must submit promotional materials to OPDP and APLB as required under FD&C Act section 506(c)(2)(B), 21 CFR 314.550 and 21 CFR 601.45. Under section 506(c)(2)(B) of the FD&C Act, the Secretary of Health and Human Services may grant accelerated approval of a drug product on the condition, among others, that the sponsor submit copies of all promotional materials related to the product during the preapproval review period and for such period thereafter as the Secretary determines to be appropriate, at least 30 days prior to dissemination of the materials. Additionally, there may be other situations when the Secretary may establish presubmission conditions on promotional materials similar to those in place for accelerated approval products (e.g., section 564(e)(4)(A) of the FD&C Act); in such situations, sponsors will be required to use the format for electronic submission outlined in section V of this draft guidance, no earlier than 24 months after it is finalized.

According to 21 CFR 314.550 and 21 CFR 601.45, unless otherwise informed by the Agency, applicants being considered for accelerated approval must submit to the Agency, during the preapproval review period, copies of all promotional materials, including both promotional labeling and ads, intended for dissemination or publication within 120 days following marketing approval (launch). Pursuant to the same regulatory provisions, after 120 days following marketing approval, unless otherwise informed by the Agency, the applicant must submit

[9] For information about OPDP reviewer assignments based on therapeutic area, refer to: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm154886.htm.

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).

The submission should include:

- Correspondence stating that it is a presubmission of promotional material(s) for an accelerated approval product (please refer to section VI.E. for additional details on what to include in the correspondence).

- A clean version of the draft promotional material(s) that does not include annotations to the label or references.

- An annotated copy of the proposed promotional material that clearly identifies the source of support for each claim (e.g., specific page and lines of the FDA-approved full prescribing information (PI) or specific page and column/paragraph from other references).

- The most current FDA-approved PI and, if applicable, the FDA-approved patient labeling or Medication 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 draft promotional materials submitted to APLB under 21 CFR 601.45, use Form FDA 2253 with line 14 checked as "Draft." Do ***not*** use Form FDA 2253 for submissions of promotional materials for accelerated approval products to OPDP under 21 CFR 314.550 or 21 CFR 601.45.

C. Promotional Materials Submitted Pursuant to Section 503C of the FD&C Act

On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85). FDAAA authorizes FDA to "require the submission of any television advertisement for a drug . . . not later than 45 days before dissemination of the television advertisement."[10] FDA intends to notify firms when television ads for a drug are subject to this submission requirement. Please refer to the draft guidance *Direct-to-Consumer Television Advertisements—FDAAA DTC Television Ad Pre-*

[10] FDAAA section 901(d)(2). This provision was initially designated as section 503B of the FD&C Act, and codified at 21 U.S.C. 353b. On November 27, 2013, the Drug Quality and Security Act [of 2013] (DQSA), Public Law 113-54, was enacted. Section 102(a) of the DQSA redesignated section 503B as section 503C of the Act, codified at 21 U.S.C. 353c.

Dissemination Review Program for recommendations regarding the components of a pre-dissemination review package.[11]

D. Promotional Materials Submitted Voluntarily for Advisory Comments

Section 21 CFR 202.1(j)(4) provides firms with a voluntary opportunity to submit promotional materials to FDA for advisory comment prior to the dissemination or publication of those promotional materials. Firms may request advisory comments on draft promotional pieces and receive comments in writing from the Agency. Because this process is intended to provide input prior to dissemination or publication, if the Agency learns that the submitted materials, or substantially similar claims or presentations, have been disseminated or published—including after submission for comments—the Agency will generally not review the materials under the advisory process.

1. Requests for Advisory Comments on Draft Promotional Materials Other Than DTC TV Ads Under 21 CFR 202.1(j)(4)

"Launch materials" are draft promotional materials that are voluntarily submitted by a firm to OPDP or APLB 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.

Requesting advisory comments on promotional materials prior to launch is encouraged. Review of core launch materials is a high priority for Agency reviewers. Core launch materials generally include:

- One comprehensive promotional labeling piece directed toward professionals (e.g., sales aid, visual aid, detail aid, or exhibit panel (if there is a major conference within the launch phase)), limited to 12 or fewer pages.

- One advertisement directed toward professionals (e.g., journal ad), limited to four or fewer pages, not including the PI or brief summary.

- One comprehensive direct-to-consumer (DTC) labeling piece (e.g., patient brochure), limited to 12 or fewer pages.

- One DTC advertisement (e.g., magazine ad), limited to four or fewer pages, not including the brief summary.

[11] The draft guidance *Direct-to-Consumer Television Advertisements—FDAAA DTC Television Ad Pre-Dissemination Review Program* is available on the OPDP Regulatory Information webpage. The draft guidance is not for implementation. When final, it will represent the Agency's current thinking on section 503C.

- A professional and/or DTC product website (limited to 12 printed pages each) or electronic sales aid if it is a derivative (i.e., contains similar claims and/or presentations) of a comprehensive labeling piece that is also submitted for advisory comment.

Launch materials other than those listed above (e.g., slide kits and materials longer than the page limits listed above) are considered non-core launch materials. Non-core launch materials are a lower priority than core launch materials. The Agency recommends that firms apply the Agency's comments on the core materials to non-core materials.

Non-launch materials consist of draft promotional materials that a firm voluntarily submits to OPDP or APLB for review and comment prior to their first use in the public domain but after the launch phase—i.e., after 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.

In general, the submission should include:

- Correspondence stating that it is a request for advisory comments (please refer to section VI.E. for additional details on what to include in the correspondence).[12]

- A clean version of the draft promotional material(s) that does not include annotations to the label or references.

- An annotated copy of the proposed promotional material(s) that clearly identifies the source of support for each claim (e.g., specific page and lines of the PI or specific page and column/paragraph from other references).

- The most current FDA-approved PI and, if applicable, the FDA-approved patient labeling or Medication 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 promotional material.

- If applicable, annotated references to support disease or epidemiology information, cross-referenced to the promotional material.

When submitting draft promotional materials other than TV ads for advisory comments:

[12] For draft promotional materials submitted voluntarily to APLB for advisory comment, please use Form FDA 2253 with the box in line 14 checked as "Draft." Please do ***not*** use Form FDA 2253 for submissions of draft promotional material submitted voluntarily to OPDP.

- Draft promotional materials submitted for advisory comment should be consolidated together into one submission for each intended audience (i.e., one submission with professional materials and one submission with consumer materials).

- It is also suggested that draft core launch materials be consolidated into a single submission for each intended audience rather than sending the materials piecemeal in several submissions over the course of a few days or weeks.

- In cases when the firm intends to submit professional and consumer launch core materials at around the same time, it is suggested that both submissions be sent on the same day.

- Likewise, it is suggested that draft non-core launch promotional materials be consolidated into single submissions for each intended audience to the extent possible.

- Submissions of draft DTC TV ads should not be included in submissions with other types of materials (see below for how to submit).

2. Requests for Advisory Comments on Proposed DTC TV Ads Under 21 CFR 202.1(j)(4)

The submission should include:

- Correspondence stating it is a request for advisory comments on a proposed TV ad (please refer to section VI.E. for additional details on what to include in the correspondence).

- A clean version of the storyboard of the proposed TV ad that does not include annotations to the label or references.

- An annotated version of the storyboard of the proposed TV ad highlighting which references support which claims.

- The most current FDA-approved PI and, if applicable, the FDA-approved patient labeling or Medication Guide with annotations cross-referenced to the storyboard.

- Other appropriate documentation if any of the following apply:

  - Annotated references to support product claims not contained in the PI, cross-referenced to the storyboard.

  - If the advertisement identifies a person as an actual patient (e.g., a spokesperson) or actual healthcare professional, a signed statement by that person verifying that he or she has in fact used or prescribed the drug product for the advertised indication, and is not merely an actor or model.

  - Verification, in the form of a signed statement by the translator, that an official translation of a foreign-language TV ad is accurate.

- Annotated references to support disease or epidemiology information, cross-referenced to the storyboard.

- Optionally, submissions for advisory review may include a video or animatic of the proposed TV ad. If included, the video or animatic should be in an acceptable file format.[13]

Materials unrelated to a proposed TV ad being submitted for advisory review should not be included in the review package. However, more than one TV ad proposal for a particular indication for a product may be submitted in the same review package.

E. Resubmissions

After FDA has responded to a request for advisory comments or commented on an accelerated approval presubmission, firms may revise and resubmit draft materials.

In general, the resubmission should include:

- Correspondence stating that it is a request for advisory comments on a revised submission (please refer to section VI.E. for additional details on what to include in the correspondence).

- A clean version of the draft promotional material(s) that does not include annotations to the label or references.

- An annotated copy of the proposed promotional material that clearly identifies the source of support for each claim (e.g., specific page and lines of the PI or specific page and column/paragraph from other references).

- The most current FDA-approved PI and, if applicable, the FDA-approved patient labeling or Medication Guide with annotations cross-referenced to the proposed promotional material.

- If applicable, annotated references to support disease or epidemiology information, 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.

F. General Correspondence

[13] The specification for industry *Specifications for File Format Types Using eCTD Specifications* is available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM347471.pdf.

General correspondence includes any correspondence submitted to FDA that may or may not reference a specific drug product application, and that does not fall into one of the other categories (e.g., 2253 submission, request for advisory comments). Please note that complaints should not be submitted under the category of "general correspondence." Examples of types of correspondence to submit under this category include the following:

- Letters in which a firm informs OPDP or APLB of an error that occurred in its promotional piece(s) or activities for its drug product(s).

- Safety update letters in which a firm informs OPDP or APLB that it will promptly revise all of its promotional materials for a particular drug(s) to be consistent with new safety information added to the product labeling.[14]

- General responses to comments from FDA provided in response to advice (advisory or general) when no revised materials are included and there is no further request from the firm to FDA for advisory comments (include Marketing & Advertising (MA) number).[15]

- Notifications from a firm to FDA that it plans to disseminate or publish promotional materials for accelerated approval products previously submitted as required under 21 CFR 314.550 or 601.45 prior to receipt of comments by FDA (e.g., after 30 days for a non-launch presubmission, or after application approval for a launch submission).

- Notifications from a firm regarding agreements with other companies for the promotion of the product.

- Notifications from a firm regarding a change in contact information.

The submission should include:

- Correspondence stating that it is a general correspondence (please refer to section VI.E. for additional details on what to include in the correspondence).

G. Amendments (Submission of Previously Missing or Rejected Materials)

If a previous request for advisory comments or 2253 submission to FDA is missing one or more promotional materials, these materials should be submitted as amendments.

For requests for advisory comments, the submission should include:

[14] This type of correspondence is not necessary if the firm notifies FDA in another correspondence (e.g., a presubmission for accelerated approval products) that it intends to comply with 21 CFR 314.70(a)(4) or 21 CFR 601.12(a)(4).

[15] The MA number is the tracking number that CDER uses to identify a submission. CBER uses the *CBER secondary number*. When the term *MA number* is used in this guidance, it refers to both the MA number and CBER secondary number, as applicable.

- Correspondence stating that it is an amendment that includes accompanying materials that were previously missing (please refer to section VI.E. for additional details on what to include in the correspondence).

- Promotional materials that were omitted from a previous submission to FDA.

- Annotated copy of the promotional materials that were omitted from a previous submission to FDA.

- The most current FDA-approved PI and, if applicable, the FDA-approved patient labeling or Medication Guide with annotations cross-referenced to the proposed promotional material.

- If applicable, annotated references to support disease or epidemiology information, cross-referenced to the proposed promotional piece that was previously omitted from a submission to FDA.

- If applicable, annotated references to support product claims not contained in the PI, cross-referenced to the proposed promotional material.

If FDA notifies a firm that promotional materials are missing from a previous 2253 submission that was submitted in paper or non-eCTD format, the firm should resubmit the entire 2253 submission rather than submitting an amendment. In these situations, if part of a 2253 submission is rejected (e.g., a video does not play), the entire 2253 submission should be resubmitted.

If the 2253 submission was in eCTD format, the firm should submit an amendment and include the following:

- Correspondence stating that it is an amendment that includes accompanying materials that were previously missing or rejected (please refer to section VI.E. for additional details on what to include in the correspondence).

- Promotional materials that were missing or rejected from a previous submission to FDA; the firm does not need to resubmit the entire 2253 submission.

  Example: A firm submits a request for advisory comments on launch promotional materials 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. FDA contacts the firm to notify it that one promotional material is missing from the submission and provides the MA number. The firm should then 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.

H. Withdrawal Requests

A firm may request to withdraw a previous submission to FDA. No materials are submitted with such a request.

Because submission of promotional materials for accelerated approval products is required under 21 CFR 314.550 and 601.45, firms should only use a withdrawal request for such materials if the firm does not plan to disseminate/publish the promotional materials.

The submission should include:

- Correspondence stating that it is a withdrawal request (please refer to section VI.E. for additional details about what to include in the correspondence).

  Example 1: A firm submits draft promotional materials for advisory review for its product (not approved under the accelerated approval regulations at 21 CFR 314.510 or 601.41) and later decides to disseminate the promotional materials without waiting for FDA advisory comments. The firm should notify FDA of its intent to withdraw the advisory request. The subject line of the correspondence should note that the submission is a withdrawal request and include the date of the advisory request or MA number.

  Example 2: A firm submits draft promotional materials for advisory review for its product (not approved under the accelerated approval regulations at 21 CFR 314.510 or 601.41) and later decides not to disseminate the promotional material. The firm should notify FDA of its intent to withdraw the request for advisory comments. The subject line of the correspondence should note that the submission is a withdrawal request and include the date of the advisory request or MA number.

  Example 3: A firm submits draft non-launch promotional materials for its product approved under the accelerated approval regulations at 21 CFR 314.510 or 601.41 and, two weeks later, decides that it does not intend to disseminate the promotional material. The firm should notify FDA of its intent to withdraw the submission. The subject line of the correspondence should note that the submission is a withdrawal request and include the date of the submission or MA number.

I. Response to Untitled Letter or Warning Letter

A response to an untitled letter or a warning letter is a correspondence type that includes a firm's initial response or additional correspondence pertaining to an untitled letter or warning letter from FDA regarding promotion.

The submission should include:

- Correspondence stating that it is a response to an untitled letter or warning letter. This response may include the firm's initial or subsequent responses. (Please refer to section VI.E. for additional details on what to include in the correspondence.)

- Corrective piece(s), if applicable.

J. Response to Information Request

FDA may issue a letter of inquiry to firms when investigating potentially violative activity. The firm's response to a letter of inquiry is considered a *response to an information request*. FDA will notify the firm when a response should be considered a response to information request. The correspondence should state that it is a response to an information request (please refer to section VI.E. for additional details on what to include in the correspondence). The correspondence should include the firm's response to the questions and issues raised in FDA's letter of inquiry, including any materials FDA has requested.

K. Reference Document

Reference documents are annotated references or annotated promotional materials that were missing from a previous submission to FDA. New promotional materials should not be included in this type of submission.

The submission should include:

- 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). Please refer to section VI.E. for additional details on what to include in the correspondence.

- Annotated references, annotated promotional materials, and/or annotated labeling.

  Example: A firm submits a request for advisory comments for non-launch materials that includes two clean copies of promotional materials. However, the submission does not include annotated copies of the promotional materials or annotated references. FDA notifies the firm and provides the MA number. The firm should submit the missing 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.

L. Complaints

Please note that complaints about prescription drug promotion are not accepted in eCTD, and they should only be submitted as paper hard copies.[16] Please submit complaints regarding professional and consumer materials separately. A duplicate copy of the submission should be provided. Please do not include Form FDA 2253 or Form FDA 356h.[17]

[16] If applicable, an electronic copy of a TV or radio ad in an acceptable file format (e.g, a CD containing a .wmv or .wma file) may be included with a complaint.

[17] Form FDA 356h is an Application to Market a New or Abbreviated New Drug or Biologic for Human Use.

Please include the following:

- Correspondence stating that it is a complaint. Please include the drug, manufacturer, and specific regulatory concerns in the correspondence. In addition, the correspondence should include the contact name, title, address, phone, fax, and email of the person that the Agency should contact about issues related to the submission.

- Supporting information or documentation, if available.

V. FORMAT FOR SUBMISSION OF PROMOTIONAL MATERIALS IN PAPER HARD COPY

Paper copies of all promotional submission types will be accepted up until 24 months following publication of the final version of this guidance. Beginning 24 months after this guidance is finalized, paper copies will no longer be accepted for postmarketing submissions made pursuant to the requirements in 21 CFR 314.81(b)(3)(i) or 21 CFR 601.12(f)(4) and submissions of promotional materials for accelerated approval products and other products where such submissions are required for approval (see section VI for further discussion). If paper hard copy materials are submitted, please use tables 1 and 2 to determine the number of paper hard copy materials to submit for each submission type. Please note that complaints are not accepted in eCTD and they should only be submitted as paper hard copies. If a submission is submitted electronically in eCTD, paper copies should not also be submitted, unless specifically requested.

Table 1: Number of Paper Hard Copies for Various Submission Types Based on Recipient

Type of Submission	**Number of Paper Hard Copies**	
	If Recipient is OPDP	**If Recipient is APLB**
Voluntary advisory submission (not a TV ad)	3	2
Voluntary advisory submission of a TV ad	10*	2*
Presubmission of promotional materials for accelerated approval products	3	2
503C TV ad	12*	2*
Resubmission	3	2
General correspondence	2	2
Amendment	3	2
Withdrawal request	2	2
Response to notice of violation or warning letter	2	2
Response to information request	2	2
Reference document	3	2
Complaint	2	2

* If a video is provided, only one copy of the video is necessary.

Table 2: Number of Paper Hard Copies of Promotional Materials to Submit in Fulfillment of the Postmarketing Reporting Requirements (Form FDA 2253 Submissions)*

2253 Submissions	Number of Paper Hard Copies
If the promotional material(s) mentions a single product	2
If the promotional material(s) mentions multiple products	3

** The number of copies is the same for OPDP and APLB. Note that beginning 24 months after this guidance is finalized, pursuant to section 745A(a) of the FD&C Act, firms will no longer be able to submit these promotional materials in paper hard copy.*

A. Submitting Hard Copy Promotional Materials to OPDP

Please send paper hard copies to the following address:

Office of Prescription Drug Promotion
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

For time-sensitive materials, please confirm receipt of the submission with a phone call to the OPDP project manager at (301) 796-1200 or by email at CDER-OPDP-RPM@fda.hhs.gov.

For promotional materials other than 503C TV advisories,[18] OPDP suggests applying an "OPDP" sticker or other prominent directional notation to the exterior of packages submitted to OPDP to help avoid misdirection of promotional materials. If it is not possible to add this notation to the exterior of the package, OPDP recommends adding a prominent directional notation (e.g., sticker, rubber stamp, etc.) to the cover letter itself.

B. Submitting Hard Copy Promotional Materials to APLB

Please send paper hard copies to the following address:

Advertising and Promotional Labeling Branch, HFM-602
Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71 – G112
Silver Spring, MD 20993-0002

[18] The draft guidance *Direct-to-Consumer Television Advertisements—FDAAA DTC Television Ad Pre-Dissemination Review Program* provides recommendations specific to 503C TV ads. The draft guidance is not for implementation. When final, it will represent the Agency's current thinking on section 503C.

Any questions for APLB may also be addressed to APLB by phone at (240) 402-9158.

VI. FORMAT FOR SUBMISSION OF PROMOTIONAL MATERIALS ELECTRONICALLY

This section provides information on specific aspects of how to submit promotional labeling and advertising materials to FDA electronically in eCTD format.[19] As discussed in section I, there are two types of submissions related to promotional materials that are "submissions under subsection (b), (i), or (j) of section 505 of [the FD&C] Act or subsection (a) or (k) of section 351 of the Public Health Service Act," and are, therefore, subject to the mandatory electronic submission requirement in section 745A(a) of the FD&C Act. The two types of submissions are: (1) postmarketing submissions of promotional materials using Form FDA 2253 (required by 21 CFR 314.81(b)(3)(i) and 21 CFR 601.12(f)(4)), and (2) submissions of promotional materials for accelerated approval products (required by FD&C Act section 506(c)(2)(B), 21 CFR 314.550 or 21 CFR 601.45) and other products where such submissions are required for approval. Therefore, beginning no earlier than 24 months after publication of the final version of this guidance, which, along with the eCTD Revised Draft Guidance, specifies the electronic format for those submission types, firms will be *required* to submit them electronically. As of that date, paper hard copies will no longer be accepted for such submissions.

While the other types of submissions related to promotional materials discussed in this guidance are not subject to the mandatory electronic submission requirement in section 745A(a), firms may—and are strongly encouraged to—make such submissions electronically. However, paper hard copies will still be accepted for submission types that do not fall under section 745A(a). We note that if firms do choose voluntarily to submit other materials electronically, CDER is currently only able to accept them in eCTD format using *us-regional-v3-3.dtd*.[20] Once a firm submits an application-related document in eCTD format, including but not limited to the types of documents described in this guidance, paper copies related to that application should no longer be submitted, unless specifically requested by the Agency.

In some cases, the company that holds the application for a drug collaborates with another company to promote the drug. If the company handling promotion of the drug wants to submit to OPDP or APLB using eCTD, the company should work with the application holder to ensure that both companies are using the same version of the *us-regional- backbone* file. If the submission is for OPDP, both companies will need to use the same version (for example, *us-regional-v3-3.dtd*). In addition, 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 that will result in a rejection of one of the submissions. For example a company could choose to assign a block of numbers to a particular vendor (e.g., start promotional submissions with sequence 5000).

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[19] For eCTD module 1 specifications that are discussed in this section see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm253101.htm.

[20] CBER is able to accept eCTD submissions using previous versions of the *us-regional-backbone* file until 24 months after publication of the final version of this guidance.

Please note that the eCTD format accommodates a wide range of applications and related submission types other than submissions of promotional materials. Therefore, a specific submission may not use all of the possible section-heading elements in each module. The following sections describe specific procedures for submitting promotional labeling and advertising to FDA in eCTD format, including submissions made pursuant to section 745A(a) of the FD&C Act.

A. Submission-Description Element

FDA recommends including the *submission-description* element to provide a high-level description of the purpose of the submission and to help differentiate similar types of submissions. The *submission-description* element should include the description of the type of submission and materials, the date of the submission[21], and the MA number (if the MA number has been provided in a previous communication with FDA) or CBER secondary number.

Some examples of helpful submission descriptions are listed below:

- Request for professional launch advisory for website, print ad, and sales aid 20140501
- Withdrawal request 20140405 for print ad MA61 submitted on 20140115
- Response to untitled letter 20140301 MA456
- Reference documents for professional launch advisory for print ad 20140302 MA31
- Consumer 2253 submission 20140915

B. Submission-Type and Submission-Sub-Type

For all promotional materials submitted to FDA via eCTD (including promotional materials submitted in fulfillment of the postmarketing reporting requirements), use the *submission-type* "Promotional Labeling Advertising." If promotional materials are submitted in eCTD without specifying "Promotional Labeling Advertising" as the *submission-type*, the submission may not get appropriately routed to OPDP or APLB and, as a result, there may be a delay in processing and responding to the submission.

The attribute *submission-sub-type* is used to further clarify the purpose of the submission. The following are the current valid *submission-sub-type* codes for the *submission-type* "Promotional Labeling Advertising:"

- *Original*. Use this *submission-sub-type* for all promotional materials submitted in fulfillment of the postmarketing reporting requirements (2253 submissions) and for materials that do not have a submission history with FDA. This includes original promotional materials such as requests for advisory on launch materials, requests for advisory on non-launch materials, presubmission of promotional materials for accelerated approval products, and materials submitted pursuant to 503C. Also use this code for responses to untitled/warning letters,

[21] The date format to be used is yyyymmdd (four-digit year, two-digit month, and two-digit day).

responses to information requests, and other general correspondence if no submission history with the FDA exists for the materials.

- *Resubmission.* Use this *submission-sub-type* for requests for advisory comments and presubmissions of revised promotional materials that were previously submitted as an "original" submission.

- *Amendment.* Use this *submission-sub-type* for a submission that contains additional supportive material to augment information previously submitted, e.g., the submission of promotional material that was previously missing or rejected, withdrawal requests, and submissions of annotated references. In addition, use this *submission-sub-type* for responses to untitled/warning letters, responses to information requests, and general correspondence if there was an original submission to FDA in eCTD format.

Table 3 summarizes the submission process and the *submission-sub-type* code for new submissions.

Table 3: Submission Process and Coding

Submission History[22]	**Action**	**Code for *Submission-sub-type***
Has no prior FDA submission history	Submit to eCTD with the same *submission-id* as the sequence number	• "Original"
All promotional materials submitted in fulfillment of the postmarketing reporting requirements (2253 submissions)	Submit to eCTD with the same *submission-id* as the sequence number	• "Original"
Already has an associated eCTD promotional submission	Submit to eCTD with the same *submission-id* as the original promotional submission	• "Resubmission" for resubmissions • "Amendment" for amendments; withdrawal requests; reference documents; responses to untitled letters/warning letters and information requests; and general correspondence
Has a paper hard-copy submission history only	Do not submit to eCTD	• Submit using paper hard-copy process

[22] The submission history is defined by the format through which the original submission was made. For example, if a 2253 submission was received in paper format, the entire submission is considered to be "paper" and all amendments to that submission should be made in paper. If a submission is received in eCTD format, all amendments to the submission should be made in eCTD format.

C. Form Element

For promotional materials submitted in fulfillment of the postmarketing reporting requirements, use *form-type* Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use) and submit this form in section 1.1. For cases where promotional material(s) mention multiple products,[23] include the attachment listing the other referenced products as a leaf with Form FDA 2253 in section 1.1.

D. Promotional Audience Type

When providing information in module 1.15, reference the leaves at the lowest heading elements. For example, the *m-1-15-promotional-material* heading element needs an attribute of *promotional-material-audience-type.* When a leaf is referenced in any subsection of module 1.15, provide the attribute as a coded value from its corresponding attribute list (promotional-material-audience-type.xml). The current valid codes for *promotional-material-audience-type* are:

- *Consumer*, for promotional materials directed to consumers; and
- *Professional*, for promotional materials directed to healthcare professionals.

E. Correspondence Related to Promotional Materials (Section 1.15.1)

Submit the correspondence relating to promotional materials as an individual portable document format (PDF) file in the appropriate subsection of 1.15.1. Firms will need to submit a correspondence for all submission types listed in section 1.15.1. A separate cover letter should not be submitted in section 1.2. Please note that firms should not submit a correspondence or a cover letter with 2253 submissions.[24] In some cases, the correspondence may be the actual response and the only file necessary for the submission (e.g., response to untitled letter, response to an Agency communication, or a general correspondence). Correspondences submitted to section 1.15.1 should include the following:

- Subject line describing the reason for the submission, the NDA/ANDA/BLA number, proprietary name/established name (dosage form), and the name of the TV ads (if applicable). Examples of acceptable descriptions to be included in the subject line include the following:
    - Request for Advisory Comments on Launch Materials
    - Request for Advisory Comments on Non-Launch Materials
    - Presubmission of Launch Promotional Materials for Accelerated Approval Product
    - Presubmission of Non-Launch Promotional Materials for Accelerated Approval Product
    - Promotional Materials Submitted Pursuant to Section 503C
    - Response to Untitled Letter

[23] Please refer to section VI.J. regarding submitting promotional materials that reference more than one application.
[24] If, however, a firm is withdrawing a Form FDA 2253 submission, it must submit a correspondence withdrawing the submission in section 1.15.1.9.

- Response to Warning Letter
- Response to Information Request
- Amendment
- Withdrawal Request
- Submission of Annotated References
- General Correspondence

The body of the correspondence should include the following information:

- Regulatory description of the submission.

- Statement that the submission is virus free with a description of the software (name, version, and company) used to check the files for viruses.

- A list of all promotional materials included in the submission with the material type, material ID, and description for each item listed.

- A concise description of use of the promotional material(s), if applicable.[25]

- Whether the submission is for a "launch" or "non-launch."

- If the submission is for a launch, whether the promotional materials are "core" or "non-core."

- Whether the submission is subject to 21 CFR 314.550, 601.45 regulations, or section 503C of the FD&C Act.

- Whether the submission is a TV ad.

- If the submission is the initial response to an untitled letter or warning letter, a list of all promotional materials (with the 2253 submission date) for the drug product(s) that contain violations similar to those described in the letter.

- Whether the submission contains healthcare professional-directed materials or consumer-directed materials.

- Where applicable, whether the Agency has previously commented on the promotional material(s); the comment date; and the Marketing, Advertising and Communications Management Information System (MACMIS), MA number, or CBER secondary number.

- The name, title, address, phone, fax, and email of the individual the Agency should contact about issues related to the submission. If there are separate regulatory and technical points of contact, please include this information for both individuals.

[25] Please refer to section VII.C. for additional details.

F. Materials (Section 1.15.2)[26]

1. Attributes

Submit promotional labeling and advertising materials as individual files in an approved file format in section 1.15.2. When providing information in a subsection of module 1.15.2 materials, three attributes are needed: *promotional-material-doc-type*, *promotional-material-type*, and *material-id*. An additional optional attribute, *issue-date*, should only be provided when the *promotional-material-doc-type* is a promotional 2253 submission. The attribute *promotional-material-doc-type* indicates the purpose of the promotional submission and needs to be provided with the *m1-15-2-materials* heading element. Provide the attributes as coded values from their corresponding attribute list (promotional-material-doc-type.xml). Table 5 shows the current valid codes for *promotional-material-doc-type*.

Table 5: Promotional Material Document Types and Descriptions

Promotional Material Document Type	Description
Promotional 2253	Form and materials required from submitter at initial dissemination of labeling as well as initial publication of an advertisement.
Request for Advisory Launch	Voluntary submission of launch promotional materials for FDA review and comment sent prior to dissemination/publication.
Request for Advisory Non-Launch	Voluntary submission of non-launch promotional materials for FDA review and comment sent prior to dissemination/publication.
Presubmission Accelerated Launch	Promotional materials intended to be used in the first 120 days after approval that are submitted to FDA prior to dissemination/publication as required by 21 CFR 314.550 and 601.45.
Presubmission Accelerated Non-Launch	Promotional materials intended to be used after the 120-day post-approval period that are submitted to FDA prior to dissemination/publication as required by 21 CFR 314.550 and 601.45.
Pre-Dissemination Review of Television Ads	TV ads submitted to FDA for pre-dissemination review in compliance with section 503C of the Federal FD&C Act.

The attribute *promotional-material-type* indicates the type of media/delivery method of the promotional material and should be provided with the *m-1-15-2-1 material* heading element.

[26] If including multiple promotional materials in one submission, please refer to section VI.I. If submitting promotional materials that reference more than one application, see section VI.J.

Provide the attributes as coded values from their corresponding attribute list (promotional-material-type.xml).[27]

The *material-id* attribute may consist of letters, numbers, or both, and should not exceed 30 characters. The *issue-date* attribute, if applicable, should follow the date format as yyyymmdd (four-digit year, two-digit month, and two-digit day).

2. Clean Version of Submitted Materials (Section 1.15.2.1.1)

For draft promotional materials submitted (1) voluntarily for advisory comment, (2) as required under section 503C of the FD&C Act, or (3) under 21 CFR 314.550 or 601.45, submit clean versions of the promotional materials (i.e., versions not including annotations to the label or references) in section 1.15.2.1.1.

Clean versions of corrective pieces should also be submitted in section 1.15.2.1.1 using the eCTD "replace" operation.

For promotional materials submitted in fulfillment of the postmarketing reporting requirements, clean final versions of the promotional materials without any annotations must be submitted in section 1.15.2.1.1.

3. Annotated Version of Promotional Materials (Section 1.15.2.1.2)

For draft promotional materials submitted (1) voluntarily for advisory comment, (2) as required under section 503C of the FD&C Act, or (3) under 21 CFR 314.550 or 601.45, submit annotated versions of the promotional materials (i.e., versions that are cross-referenced to the product labeling and, if applicable, references) in section 1.15.2.1.2.

Annotated versions of corrective pieces should also be submitted in section 1.15.2.1.2 using the eCTD "replace" operation.

For promotional materials submitted in fulfillment of the postmarketing reporting requirements, firms may choose to submit annotated versions of the promotional materials in section 1.15.2.1.2 that are cross-referenced to the product labeling and, if applicable, references. References improve the efficiency of review.

Firms should highlight and annotate the materials with a cross reference to the product labeling or references. When product labeling or other references are used to support a claim or presentation in proposed promotional materials, hypertext links should be provided in the annotated promotional material to the page/specific lines that contain the supporting information.

[27] The current codes for *promotional-material-type*, as well as the codes for other attributes, are available on the FDA website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm253101.htm.

G. Product Labeling (Section 1.14.6 and Section 1.15.2.1.3)

1. Product Labeling Accompanying Form FDA 2253 Submissions (Section 1.14.6)

Form FDA 2253 specifies that the most current product labeling accompany the submission. Firms must submit the most current product labeling, as required in 21 CFR 314.81(b)(3)(i), to section 1.14.6. For promotional labeling pieces, this is the PI that accompanies the promotional materials. The required format for the PI is PDF.[28]

2. Annotated Product Labeling (Section 1.15.2.1.3)

For draft promotional materials submitted (1) voluntarily for advisory comment, (2) as required under section 503C of the FD&C Act, or (3) under 21 CFR 314.550 or 601.45, include the annotated product labeling in section 1.15.2.1.3.[29] Firms should highlight and annotate, with a cross-reference to the promotional materials, the sections of the product labeling that are referred to in the promotional materials. When product labeling is used to support a claim or presentation in proposed promotional materials, hypertext links should be provided to the page/specific lines that contain the supporting information.

For promotional materials submitted in fulfillment of the postmarketing reporting requirements, firms may choose to provide the annotated product labeling with hypertext links.[30]

H. Annotated References (Section 1.15.2.1.4)

If references are provided, submit each reference as an individual PDF file and place it in section 1.15.2.1.4. Firms should highlight and annotate, with a cross reference to the promotional materials, the sections of the full reference that are referred to in the promotional materials. When a reference is used to support a claim or presentation in proposed promotional materials, firms should provide, in the annotated promotional material, hypertext links to the page and the specific lines of the reference that contains the supporting information.

For promotional materials submitted in fulfillment of the postmarketing reporting requirements, firms may choose to provide references with hypertext links. References improve the efficiency of review.

[28] Firms may choose to submit the current product labeling with each 2253 submission. Alternatively, once product labeling is submitted to section 1.14.6 with a 2253 submission, firms may cross reference the current product labeling within the XML backbone. If firms choose to reference the current product labeling within the XML backbone, they should 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). Refer to section VI.K. for recommendations regarding leaf titles.

[29] Even if the submission does not include annotations to the label or a part of the label, firms should still include the entire label in section 1.15.2.1.3.

[30] Annotated labeling submitted in fulfillment of the postmarketing reporting requirements must be included as a PDF file in section 1.15.2.1.3. The current product labeling must still be submitted in section 1.14.6.

I. Including Multiple Promotional Materials in One Submission

For draft promotional materials voluntarily submitted for advisory comment or submitted as required under 21 CFR 314.550 or 601.45, if multiple promotional materials are included in one submission, each of these materials is to be submitted with its own clean version, annotated version, annotated labeling, and annotated references. The following example shows how to submit multiple promotional materials in one submission in section 1.15 for advisory comments.

1.15 Promotional material (Professional)
1.15.1 Correspondence relating to promotional materials
1.15.1.1 Request for advisory comments on launch materials
Request for professional launch advisory for sales aid and print ad 20140501
1.15.2 Materials (Request for Advisory Launch)
1.15.2.1 Material (Sales Aid)(65NO35482)
1.15.2.1.1 Clean version
Sales aid 65NO35482 Considerations for treatment 20140501 CLEAN
1.15.2.1.2 Annotated version
Sales aid 65NO35482 Considerations for treatment 20140501 ANNOTATED
1.15.2.1.3 Annotated labeling version
PI annotated to sales aid
1.15.2.1.4 Annotated references
Reference 1 Smith et al. for sales aid
1.15.2.1 Material (Print Ad)(77UY6788)
1.15.2.1.1 Clean version
Print ad 77UY6788 A new option 20140501 CLEAN
1.15.2.1.2 Annotated version
Print ad 77UY6788 A new option 20140501 ANNOTATED
1.15.2.1.3 Annotated labeling version
PI annotated to print ad
1.15.2.1.4 Annotated references
Reference 1 Murray et al. for print ad
Reference 2 Shoon et al. for print ad

For promotional materials submitted in fulfillment of the postmarketing reporting requirements, if multiple promotional materials are included in one submission, submit clean versions of each promotional piece in section 1.15.2.1.1. The following example shows how to submit multiple promotional materials in one submission in section 1.15.

1.1 Forms
Form FDA 2253: Transmittal of Advertisements and Promotional Labeling for Drugs And Biologics for Human Use
Form FDA 2253 Professional website and print ad 20140105
1.15 Promotional material (Professional)
1.15.2 Materials (Promotional 2253)
1.15.2.1 Material (www-website)(68443439)(20130105)
1.15.2.1.1 Clean version

Website 68443439 Challenges to treatment 20140105 CLEAN
1.15.2.1 Material (Print Ad)(3945730)(20140105)
1.15.2.1.1 Clean version
Print a d 3945730 A new treatment 20140105 CLEAN

J. Submission of Promotional Materials Referencing More Than One Application (Grouped Submissions)

Firms may submit promotional pieces that promote more than one product (i.e., a multiple-product submission) as a grouped submission.[31] However, only one application type can be used in a grouped submission. Therefore, should a promotional piece apply to more than one application type (e.g., a BLA and NDA), submit the promotional piece as a separate submission for each application type (i.e., there would be two separate submissions—one for the BLA application and one for the NDA application).

K. Leaf Titles

Appropriately named "leaf titles" allow FDA reviewers to navigate through submissions and distinguish one submission from another in the eCTD viewer. A leaf title should include the MA number if it has been provided in a previous communication with FDA.

The format of the leaf title for the actual form for Form FDA 2253 submissions (placed in section 1.1) should be informative for Agency reviewers. For example, the leaf title "Form FDA 2253 Consumer print ad 20140105" is more informative and searchable than a leaf title of "2253Form." Although both examples identify the submission by type, in the first example the Agency reviewer will know the audience for the promotional material (consumer), the material type code, and the date of the submission—all without having to open the file itself.

In addition, the leaf title for the correspondence related to promotional materials (placed in section 1.15.1) should help the Agency reviewer identify the incoming submission by type. A leaf title of "Response to untitled letter 20140105 MA37" is more informative than a leaf title of "Response to untitled letter" because the former example identifies the type of correspondence, the letter date of the submission, and the MA number.

Leaf titles for each promotional piece (placed in section 1.15.2) should also be informative. For example, a healthcare professional-directed sales aid with the leaf title "Sales Aid 65NO35482 Considerations for treatment 20140102" is more informative than the leaf title "promotional piece.pdf." When displayed in the eCTD viewer, the first example immediately identifies the material type code, the material identifying number of the piece (if applicable), a description of the piece, and the date of the submission. All of this information is useful to the Agency reviewer.

[31] For instructions on assembling grouped submissions, please see http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163552.pdf.

L. Use of Operator Attributes

When using lifecycle operations:

- For resubmissions, use the "replace" operator attribute to replace the previously submitted files with the resubmission's updated files. If a firm is only resubmitting part of the original submission, the operator for the correspondence file should be "new."

- For withdrawals, submit the withdrawal request and use the "delete" operator attribute on all leaves that are affected by the withdrawal request. The operator for the correspondence file should be "new."

VII. PRESENTATION ISSUES

Because electronic images may not adequately convey the net impression of the promotional piece or the details of the intended promotional message within the piece, firms should follow the guidelines below to facilitate review by the Agency.

A. General Presentation Considerations

In general, the presentation considerations below encompass the appearance, layout, format, and visible impression of promotional materials submitted for all promotional submission types and audiences. 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. In rare instances when this is not possible, firms are to submit electronic promotional materials in a manner for which the net impression is clear and legible; likewise for the individual representations in each promotional piece.

Provide each promotional piece submitted to the Agency in electronic format as an individual file in an approved file format. If the current list of approved file formats does not allow the firm to submit a fully functional piece, the submission needs to provide the ability to view all interactive selection options as still images with annotations or notes that clearly describe the functionality of the piece.

Please note that promotional materials submitted with Form FDA 2253 to OPDP must include a representation of the actual piece that is disseminated rather than solely a proof or galley copy of the promotional piece. However, a proof or galley copy of the promotional piece may also accompany the actual piece as part of the submission in order to demonstrate layout or size presentation elements. Proof or galley copies of the promotional piece should be submitted within section 1.15.2.1.2 of module 1. This recommendation does not apply to APLB submissions.

B. Visibility of Text and Images

Promotional materials should present clear and legible text and images regardless of the format (electronic and/or physical media). While the Agency recognizes that electronic images and text

may require magnification on computer screens during the review process, 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.

C. Concise Description of Use

Each promotional piece should include a concise description of use. The description may include, but should not be limited to, the purpose of the piece, setting of use for the piece, and/or an explanation of additional materials that will be used in conjunction with the piece. The concise description of use may be presented on Form FDA 2253 under "Comments" as a comment on the electronic version of the promotional piece, as a comment on an optional proof or galley piece, and/or within the correspondence of an advisory request. A concise description of use is particularly important in situations where additional context is necessary, such as when:

- The purpose of the promotional piece is not self-evident after looking at an image of the piece or reading its title (e.g., a journal ad may be designed with an appearance similar to a booth panel).

- The promotional piece is designed for use only in conjunction with other specific promotional pieces.

- The promotional piece is designed for use in a very specific setting.

- The promotional piece (with the same material ID number) is designed for multiple uses in different and unique settings.

Concise descriptions of use may include, but should not be limited to, language such as:

- Booth panel A will be used only in conjunction with booth panels B, C, and D
- For use as a journal ad and a physician leave-behind
- Item 1 of 5 of kit
- For one-time use during [Conference Title, Month/Year]

D. Layout Indicators

Firms should submit promotional materials with clear and legible indicators for navigating through each promotional piece, as applicable. Indicators describing location and navigation elements in the piece should be presented on each electronic page or image and should not obstruct the image of the promotional materials. Indicators may include, but should not be limited to, the following:

- Front cover, back cover, inside front cover, inside back cover
- Bottom of piece or page, top of piece or page
- Front of piece, back of piece
- Page numbers
- Inserts

- Pockets and pocket content
- Tabs or section dividers
- Folds
- Blank pages or panels
- Annotations to references
- Actual size
- Clarifying the PI position

Indicators may be presented as symbols or text. A key should be provided if symbols are presented as indicators within a submission.

E. Websites, Electronic Interactive Programs, and Electronic Detail Aids

Electronic promotional material submissions including, but not limited to, websites, electronic interactive programs, and electronic detail aids should clearly display and communicate how the promotional piece will look and convey messages to the end user. Preferably, the submission should allow FDA reviewers to view and interact with the piece in the same manner as the end user. For example, still electronic images may not adequately convey how complex interactive promotional pieces convey promotional messages. Such promotional submissions may also be accompanied by a video showing manipulation of the promotional program or application.

In general, in order to comply with the postmarketing requirement for promotional materials in 21 CFR 314.81(b)(3)(i), a firm must submit its entire product website at the time of first use. If the firm then updates one page or section of the website, the firm need only submit the updated page or section with a cross-reference to the original submission of the website noted on Form FDA 2253, including the date of the original submission. If the website is substantially revised, the firm must submit the revised website in its entirety.[32]

F. Materials Requiring Physical Manipulation by the End User

Promotional materials requiring physical manipulation by the end user in order to obtain the net impression of the promotional message (and/or the details of the promotional message) should be submitted in a format that allows the Agency to view all aspects of the promotional piece. For example, the electronic submission of a lenticular refrigerator magnet may display one image if tilted left and an alternate image if tilted right. Representations for both images should be submitted in this case.

G. Three-Dimensional Promotional Pieces or Materials

Electronic submission of three-dimensional promotional objects should provide sufficient detail to allow FDA to view the promotional material from all possible views. In addition, images

[32] For detailed information regarding fulfilling regulatory requirements for postmarketing submissions of interactive promotional media, refer to the draft guidance *Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics*. When final, this guidance will represent the FDA's current thinking on this topic.

should provide adequate information to allow Agency reviewers to determine the size of the object (e.g., point size, dimensions). In rare situations, it may not be possible to accurately represent the promotional piece in an electronic format. In these situations, the best possible electronic image should be submitted electronically and a courtesy copy of the promotional piece can also be sent for the reviewer. The courtesy copy of the promotional piece should be submitted as a general correspondence and should include a reference to the electronic submission and sequence number.

H. Multi-Page Spreads[33]

Promotional materials that include text or images that span more than one page or for which the promotional message may be interpreted as spanning more than one page (e.g., a two- or three-page brochure spread) should include a clear image or representation of the entire spread within a single view. All possible spreads of a given promotional piece should be presented. In addition, electronic images of print materials and electronic materials should be presented in a manner and sequence as they would appear to the end user.

I. Kits

Electronic submission of kits should clearly indicate the components of the kit. Components of the kit that are not intended for distribution apart from the kit should be labeled as such. The accompanying Form FDA 2253 must include the material ID number or identifier for the kit, as well as the material ID number or identifier for each individual component of the kit.

J. Dimensions

All images of physical materials should include dimensions. Images of three-dimensional pieces should be identified as such in the descriptions and provide information adequate to determine height, width, and depth dimensions.

Dimensions should be presented with standard units of measure.

K. Examples of Appropriately Submitted Promotional Materials

Although not exhaustive, the following examples illustrate appropriate electronic submissions of promotional materials in terms of presentation issues:

Example 1: A firm creates a website for a new product that includes links and videos. As part of its postmarketing requirements, the firm must submit an electronic version of the product website under cover of Form FDA 2253. The website should allow the FDA reviewer to click on links within the website and view videos or other animations as an end

[33] In this guidance, the term *spread* is used to refer to adjacent pages of promotional material with related matter or connecting elements extending across the fold.

user will experience while using the site.[34] If the firm is unable to provide active links within the electronic submission, the firm should provide electronic images of each webpage in conjunction with videos.

Example 2: A firm is disseminating an electronic version of a promotional labeling piece containing a healthcare professional-directed quiz. As part of its postmarketing requirements, the firm should submit an electronic working version of the quiz under cover of Form FDA 2253. If the firm is unable to provide a working version of the quiz, the submission must include images that convey the results of selecting correct answers as well as the images resulting from incorrect answers.

Example 3: A firm submits, for advisory comments, an electronic image of a promotional mug that displays a product logo, a frequently used tagline, and a graphic that appears on the mug when hot liquid is added. The submission should include images of the front, back, inside, bottom, and sides of the mug regardless of whether any particular view contains a promotional claim or representation. In addition, the submission should also include images of the mug when hot liquid is added along with an explanation of when the images appear. Such a submission would benefit from layout indicators such as "front," "back," and "intentionally left blank," in addition to measurement indicators.

Example 4: A firm submits, for advisory comments, an electronic image of a trifold branded print brochure. The firm should present, in the following order, images of: (1) the front cover of the brochure, (2) all possible two-page spreads when the brochure is partially opened, (3) the single three-page spread when the brochure is completely opened, and (4) the back cover of the brochure. Such a submission would benefit from layout indicators such as "front panel," "rear panel," "2-panel spread," and "3-panel spread," in addition to measurement indicators.

Example 5: A firm is developing a kit for use that includes consumer-directed promotional materials that are exclusive to the kit to be submitted for advisory comments. For each piece of material included in the kit, the firm should provide a concise description for use. For example, a promotional piece that is intended only for distribution within the kit would include the following description: "Intended for distribution in consumer-directed sample kit only."

Example 6: A firm is developing a Form FDA 2253 submission for an electronic banner used within an exhibit booth. The firm should submit a working version of the banner. However, if a working version of the banner cannot be submitted, the firm should submit a video of the banner in conjunction with screen shots. This is preferable to a submission consisting only of static screen shots. For example, the submission should include a video of the banner along with screen shots that convey how the message will scroll, the time lapse for the complete scroll of the message, and any variation in the rate that the message is scrolled across a screen.

[34] A fully functional website should be submitted in an accessible format whenever possible. Firms should not send links to websites—even if they are password-protected.

Example 7: A firm is developing a Form FDA 2253 submission for a consumer-directed branded video game that is embedded within a standard website. If a working version of the game cannot be submitted using an acceptable file format, the firm should submit a video of the game being played in addition to electronic still images of the game. If the game will also be available to consumers within a conference exhibit setting, the firm should include a concise description of use disclosing this additional unique setting.