Importation of Certain FDA-Approved Human Prescription Drugs, Including Biological Products, and Combination Products under Section 801(d)(1)(B) of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

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)
Office of Combination Products (OCP)
Office of Regulatory Affairs (ORA)

September 2020
Labeling
Pharmaceutical Quality/CMC

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TABLE OF CONTENTS

Contains Nonbinding Recommendations

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

I. INTRODUCTION

This guidance describes recommended procedures to obtain a National Drug Code (NDC) for certain FDA-approved prescription drug products that are imported into the United States in compliance with section 801 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 381).[2, 3] As described in further detail in the Background section of this guidance, this guidance specifically addresses FDA-approved drugs that are also authorized for sale in a foreign country in which the drugs were originally intended to be marketed (hereinafter "multi-market approved products" or "MMA products").[4]

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health, the Office of Combination Products in the Office of the Commissioner, and the Office of Regulatory Affairs at the Food and Drug Administration.

[2] For the purposes of this guidance, *drug product* or *drug* will be used to refer to human prescription drug and biological products that are regulated as drugs, except where specific reference is made to drugs approved under section 505 of the FD&C Act (21 U.S.C. 355) or biological products licensed under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262). For the purposes of this guidance, the terms drug and drug product also refer to combination products approved under a new drug application (NDA) or biologics license application (BLA), and the term biological product also refers to combination products approved under a BLA, except where specific reference is made to such combination products.

[3] This guidance addresses biological products that are licensed pursuant to approved BLAs under either section 351(a) or section 351(k) of the PHS Act, including a biological product that was originally approved in an NDA that was deemed to be a license for the biological product (i.e. an approved 351(a) BLA) pursuant to section 7002(e)(4)(A) or section 7002(e)(4)(B) of the Biologics Price Competition and Innovation Act of 2009. This guidance is not intended to address certain biological products, such as blood and blood components, including those intended for transfusion, or allogeneic cellular or tissue-based products. As a general matter, because of differences in donor eligibility and infectious disease testing requirements, we do not expect that these products, when approved for marketing by a non-U.S. regulatory authority and originally intended for sale outside the United States, would be able to meet the requirements to obtain a U.S. license.

[4] This term is further defined for purposes of this guidance in section III.A.

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

II. BACKGROUND

This guidance is intended to outline a potential pathway by which manufacturers could obtain an NDC for an FDA-approved drug that was originally intended to be marketed in a foreign country and is also authorized for sale in that foreign country. Recently, FDA has become aware that some drug manufacturers may be interested in offering certain of their drugs at lower costs and that obtaining additional NDCs for these drugs may help them to address certain challenges in the private market. By following the procedures described in this guidance, manufacturers could obtain an NDC for an MMA product, which would provide an additional avenue through which drugs could be sold at a lower cost in the U.S. market.

Under this pathway, a manufacturer could import such a drug if, consistent with section 801(d)(1)(B) of the FD&C Act, the drug is manufactured outside the United States and the manufacturer[5] has authorized the drug to be marketed in the United States and has caused the drug to be labeled to be marketed in the United States.[6] In addition to other requirements, under section 801(a) of the FD&C Act, to be lawfully imported into the United States, drugs must not be in violation of section 505 of the FD&C Act (21 U.S.C. 355), or be adulterated in violation of section 501 of the FD&C Act (21 U.S.C. 351) or misbranded in violation of section 502 of the FD&C Act (21 U.S.C. 352).

This guidance also describes the recommended procedures for submitting certain documentation to demonstrate that the drug offered for import, although originally intended for marketing in a foreign country, is, in fact, an FDA-approved drug and meets the required specifications in the approved new drug application (NDA) or BLA, and thus may be eligible for importation under section 801(a) and (d) of the FD&C Act. In addition, this guidance describes processes for registration and listing and obtaining an NDC for such drugs.

This guidance describes recommended labeling changes for MMA products. In addition, this guidance describes the applicable requirements of section 582 of the FD&C Act (21 U.S.C. 360eee-1), as added by the Drug Supply Chain Security Act (DSCSA) (Title II of Public Law 113-54). Finally, this guidance describes importation procedures and other requirements applicable to MMA products.[7]

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[5] For purposes of this guidance, the manufacturer is the NDA or BLA holder for the MMA product.

[6] Section 801(d)(1)(B) of the FD&C Act provides that, with limited exceptions:

> [N]o drug that is subject to section 503(b)(1) [of the FD&C Act] may be imported into the United States for commercial use if such drug is manufactured outside the United States, unless the manufacturer has authorized the drug to be marketed in the United States and has caused the drug to be labeled to be marketed in the United States.

[7] The procedures outlined in this guidance are not intended to supplant existing procedures for temporary importation used to mitigate or prevent drug shortages.

III. DESCRIPTION AND LABELING OF AN MMA PRODUCT

A. Description

This guidance specifically addresses the importation of FDA-approved drugs that are also authorized for sale in a foreign country in which the drugs were originally intended to be marketed, which we are calling MMA products. For the purposes of this guidance, an MMA product is an FDA-approved prescription drug or FDA-licensed biological product, or a combination product approved in an NDA or BLA (see 21 CFR Part 3), that:

- was originally manufactured outside the United States and is authorized for marketing by another country's regulatory authority;
- is the subject of a supplement to an approved NDA or a BLA, including all the information described in section IV.A. or B. of this guidance;
- is imported into the United States and is authorized by the manufacturer (i.e., the applicant) under section 801(d)(1)(B) of the FD&C Act to be marketed in the United States;
- meets the quality standards in the approved application for marketing in the United States;
- continues to meet the quality standards for marketing in its originally intended market;[8] and,
- differs from the FDA-approved drug or FDA-licensed biological product only with regard to the labeling statement described in section III.B of this guidance.

The following sections provide a more specific description of MMA drug products, biological products, and combination products, respectively.

1. Drug Products

For purposes of this guidance, an MMA drug product is a drug product that is the subject of a supplement to an FDA-approved NDA in which the applicant demonstrates that the MMA drug product is approved by FDA, and, therefore, that the MMA drug product has the FDA-approved product's: active ingredient(s); active ingredient source(s) (including manufacturing facility(ies)), inactive ingredients; dosage form, strength(s), and route(s) of administration; container closure systems and other materials used in the production of the FDA-approved drug; and meets the specifications of the drug product, as described in the FDA-approved NDA. An MMA drug product would continue to have the same appearance as the FDA-approved product before the MMA supplement was approved; for example, an MMA drug product in solid oral dosage form would be identical in attributes including size, shape, color, imprint, and scoring.

As described in further detail in section IV of this guidance, an MMA drug product has the same formulation, manufacturing process and specifications for the active ingredients and drug product as in the chemistry, manufacturing, and controls section of the approved NDA (including any information incorporated by reference). An MMA drug product conforms to the

[8] A product's failure to meet the quality standards of the regulatory authority in its originally intended market may suggest the existence of manufacturing process control issues in the production of that product.

specifications described in the approved NDA, including the quality of active ingredients, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of the drug. To meet the specifications of the application holder's existing NDA, an MMA drug product is manufactured, packaged, labeled, and tested at the facility(ies) approved in the NDA, including specific site(s),production lines, and quality systems.

2. Biological Products

For purposes of this guidance, an MMA biological product is a biological product that is the subject of a supplement to an FDA-approved BLA (including an FDA-approved NDA that was deemed to be an FDA-approved BLA) in which the applicant demonstrates that the MMA biological product is licensed by FDA, and, therefore, that all lots of the MMA biological product have the FDA-licensed product's drug substance and drug substance source(s) (including manufacturing facility(ies); dosage form, strength, and route(s) of administration; container closure systems and other materials used in the production of the FDA-licensed biological product; and all lots of the MMA biological product meet the specifications of and comply with the FDA-approved BLA. An MMA biological product would continue to have the same appearance as the FDA-licensed product before the MMA supplement was approved; for example, an MMA biological product in liquid dosage form would be identical in attributes such as color.

As described in further detail in section IV of this guidance, an MMA biological product has the same formulation, manufacturing process and specifications for drug substance and biological product as in the chemistry, manufacturing, and controls section of the approved BLA (including any information incorporated by reference, if appropriate). An MMA biological product conforms to the specifications described in the approved BLA, including the quality of drug substances, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of the biological product. To meet the specifications of the license-holder's existing BLA, an MMA biological product is manufactured, packaged, labeled, and tested in the facility(ies) and using the manufacturing line(s) and quality system(s) used to manufacture the FDA-licensed biological product.

3. Combination Products

For purposes of this guidance, an MMA combination product is a combination product, as defined in 21 CFR 3.2(e), except for any combination product that includes a biological product not within the scope of this guidance (see footnote 3). An MMA combination product is a combination product that is the subject of a supplement to an FDA-approved BLA or NDA and for which the product as a whole, including the constituent parts, meets the specifications of the FDA approval.[9]

[9] If a drug or biological product is a constituent part of a "cross-labeled" combination product that includes a separately distributed device constituent part (see 21 CFR 3.2 (e)(3) and 3.2(e)(4)), the MMA product would be the drug or biological product constituent part of the combination product. The separately distributed device constituent part would not be an MMA product.

For purposes of this guidance, an MMA combination product would contain a drug and/or biological product constituent part that meets the specifications in the approved application as set forth in the applicable paragraphs of section III.A.1. or III.A.2. of this guidance, above. For combination products containing a device constituent part, the device constituent part of an MMA combination product is the same device constituent part that is included in the FDA-approved application for the combination product. The components, manufacturing materials, and specifications of the device constituent part of an MMA combination product are identical to those used in the manufacture of the FDA-approved combination product, and the methods used in, and the equipment, facilities, and testing and other controls used for, the design, manufacture, packaging, labeling, and storage of the combination product, including the device constituent part, are the same as those for the FDA-approved combination product. An MMA combination product must comply with current good manufacturing practice requirements set forth in 21 CFR Part 4, Subpart A.

B. Labeling

Under the procedures described in this guidance, an MMA product, like any FDA-approved prescription drug, must bear the FDA-approved labeling, including the proprietary name (if any) and the nonproprietary name,[10] the container label, and the carton or package labeling, and be accompanied by FDA-approved labeling (e.g., the Prescribing Information) as required under the FD&C Act and implementing regulations. (See, e.g., 21 U.S.C. § 352(e), (f); 42 U.S.C. § 262(a)(1)(B)(i); 21 CFR 201.5; 21 CFR 201.57(a)(2); 21 CFR 201.80(a)(1)(i); 21 CFR 201.100(b), (c); 21 CFR 600.3(k); 21 CFR 610.60; 21 CFR 610.61).

In addition, FDA recommends, as described in the following paragraphs, that the container label and carton or package labeling of an MMA product bear features that allow the MMA product to be easily distinguishable from non-MMA products and that the container label, carton or package labeling, and labeling on or within the package from which the MMA product is dispensed (except for FDA-approved patient labeling) include a statement to differentiate the MMA product from non-MMA products.

For the container label and carton or package labeling, FDA recommends that the MMA product bear a narrow, transparent colored stripe, which we generally recommend to be yellow,[11] printed horizontally within the top one-half of the container label and carton or package labeling. The shade of color used in the stripe should provide sufficient contrast with the background of the container label and carton or package labeling so that the stripe will be easily visible when selecting the product from the pharmacy shelf. Likewise, the stripe should be of a sufficient width relative to the size of the container label and carton or package labeling so that the MMA product will be easily visible when selecting the product from the pharmacy shelf.

[10] The nonproprietary name designated by FDA in the license for a biological product licensed under the PHS Act is its proper name (section 351(a)(1)(B)(i) of the PHS Act (42 U.S.C. 262(a)(1)(B)(i)) and § 600.3(k) (21 CFR 600.3(k)).

[11] Other colors should be considered in situations where a yellow stripe may not provide adequate contrast against other coloring used on a container label or carton or package labeling, or where a yellow stripe may not allow for adequate legibility of the text on the container label or carton or package labeling.

The container label, carton or package labeling, and Prescribing Information should also include a statement to help pharmacists distinguish an MMA product. The container label and carton or package labeling should prominently display within the stripe the statement or similar statement, "Imported following the procedures recommended in FDA Guidance: see [insert current link to this guidance on FDA.gov]." In cases where the container label does not have adequate space for the statement, the statement should be affixed to the container by other prominent means such as a peel-back label. In the rare event where prominent placement within the stripe is not feasible, FDA recommends that this statement appear on the principal display panel of the container label and carton or package labeling. The stripe and statement on the container label and carton or package labeling should be sufficiently prominent to help a pharmacist readily distinguish the MMA product without obscuring required or recommended information (e.g., information that will reduce the risk of medication errors and ensure safe administration of the drug).[12]

FDA recommends that the following statement or similar statement should be included in the Prescribing Information: "Imported following the procedures recommended in FDA Guidance: see [insert current link to this guidance on FDA.gov]. FDA recommends that this statement appear in the HOW SUPPLIED/STORAGE AND HANDLING section for products subject to 21 CFR 201.56(d) and 201.57, or in the HOW SUPPLIED section for products subject to 21 CFR 201.56(e) and 201.80. FDA recommends that this statement be associated with the NDC number(s) of MMA product(s) (e.g., an asterisk can be placed after each MMA product NDC number which will refer to the recommended statement in the HOW SUPPLIED/STORAGE AND HANDLING section for products subject to 21 CFR 201.56(d) and 201.57).

IV. SUBMISSION OF A SUPPLEMENT FOR AN MMA PRODUCT

This section describes the process by which the holder of an approved application may obtain marketing approval of an MMA product and describes the recommended information to be submitted with the appropriate supplement for the labeling changes to the approved application. An applicant must notify FDA of a change to an approved application in accordance with all statutory and regulatory requirements. FDA recommends that an applicant seeking to market an MMA product under an NDA or a BLA submit a supplement, generally a labeling supplement, under 21 CFR 314.70 or 601.12(f), respectively. The labeling statement discussed in this guidance would not be appropriately submitted in an annual report under 21 CFR 314.70(d) or 601.12(f)(3). FDA also recommends that the cover letter for the supplement note that the supplement is an "MMA supplement."

FDA recommends that the information supporting the supplement be provided by attestation, as described in detail below. The information contained in the attestation accompanying the NDA or a BLA supplement should be known to the applicant. In addition, the drug or biological product should not have left the control of the applicant prior to or during the manufacturing, packaging, labeling, and testing processes described in sections A. and B. below to which the applicant attests.

[12] FDA has issued draft guidance that, when final, will represent FDA's current thinking on this topic. See FDA Draft Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (Apr. 2013). For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

A drug offered for import as an MMA product without an approved supplement may be subject to refusal of admission.

In the subsections below, FDA provides recommendations for submission of NDA supplements and BLA supplements. Since there are some differences in the information accompanying the submissions for each product type, and for ease in quickly identifying the applicable recommendations for the different supplements, the sections are divided by type of application.

A. NDA Supplements

In an NDA supplement seeking to change the FDA-approved labeling for an MMA product, FDA recommends that the following information be submitted. The supplement should include information to demonstrate that a product originally intended for sale in another country is the FDA-approved product and is manufactured in accordance with the FDA-approved NDA, with the exception of the limited labeling differences discussed in this guidance. The information about the MMA product should also establish that the composition of the drug product, as well as the entirety of the manufacturing process, from active pharmaceutical ingredient through finished product, meets all of the specifications in the chemistry, manufacturing, and controls section in the NDA for the FDA-approved drug product (21 CFR 314.50(d)(1)) and any submission incorporated by reference (e.g., Type II drug master file). FDA expects to review the addition of the labeling statement discussed in this guidance to ensure it does not distract from, interrupt, or distort the required and recommended information in the labeling.

FDA recommends that the supplement include an attestation in the cover letter stating that the MMA product has the active ingredient(s), active ingredient source (including manufacturing facility(ies)), inactive ingredients, dosage form, strength(s), route(s) of administration, and device constituent part(s) (as applicable) described in the NDA. The application also should include information specifying the non-U.S. regulatory authority (Health Canada, the European Medicines Agency, etc.) that has authorized the drug product for marketing in a non-U.S. jurisdiction. The attestation should include the applicant's commitment that the MMA product will continue to meet the quality standards for marketing in its originally intended market. The attestation should establish that the MMA product conforms to the information described in the approved application regarding the quality of active ingredients, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of the drug. The attestation should establish that the MMA product, including the device constituent part (as applicable), is manufactured, packaged, labeled, and tested at the facility(ies) approved in the NDA, including specific site(s), production lines, and quality system(s). The attestation described above and executed batch records described below would generally be considered an acceptable way to demonstrate in the supplement that the MMA product is the FDA-approved product.

The supplement should include the executed batch record, including the certificate of analysis (COA), for at least one commercial scale batch of the MMA product produced using each of the intended manufacturing line(s). This analysis should be compared to the analysis completed for a recently manufactured commercial batch produced and released for distribution to the U.S. market under the approved NDA.

B. BLA Supplements

In a BLA supplement seeking to change the labeling for an MMA product, FDA recommends that the following information be submitted.[13] The supplement should include information to demonstrate that a product originally intended for sale in another country is the FDA-licensed product and is manufactured in accordance with the FDA-approved BLA, with the exception of the limited labeling differences discussed in this guidance. The information about the MMA product should also demonstrate that the lots of the MMA product intended for importation meet all of the specifications in the chemistry, manufacturing, and controls section of the approved BLA for the biological product. (See 21 CFR 601.3). FDA expects to review the labeling statement discussed in this guidance to ensure it does not distract from, interrupt, or distort the required and recommended information in the labeling.

For licensed biological products, in order to support a demonstration that the MMA product is the FDA-licensed biological product, the supplement should include an attestation in the cover letter that the MMA product is the FDA-licensed product, including device constituent part(s) (as applicable), and is manufactured in accordance with the FDA-approved BLA, with the exception of the limited labeling differences discussed in this guidance. The application should also include information specifying the non-U.S. regulatory authority (Health Canada, the European Medicines Agency, etc.) that has authorized the biological product for marketing in a non-U.S. jurisdiction. The attestation should include the applicant's commitment that the MMA product will continue to meet the quality standards for marketing in its originally intended market. The attestation should establish that the MMA product conforms to the information in the FDA-approved BLA to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of the biological product. In the supplement, the applicant should include information and data demonstrating that the lots of the MMA product intended for importation are, and will continue to be manufactured, packaged, labeled, and tested in the FDA-licensed biological product's facilities using the same manufacturing line(s) and quality system(s) that are used to manufacture the FDA-licensed biological product, including the device constituent part (as applicable). The attestation described above and executed batch records described below would generally be considered an acceptable way to demonstrate in the supplement that the MMA product is the FDA-licensed product.

The supplement should include an executed batch record, including the COA for a recently manufactured commercial batch of the MMA product, and the batch record should contain all relevant information regarding the manufacturing process and controls to support the demonstration that the batches of the MMA product intended for importation are the FDA-licensed biological product. This analysis should be compared to the analysis completed for a recently manufactured commercial lot produced and released for distribution to the U.S. market under the approved BLA.

[13] Such changes to the approved labeling of a biological product typically are submitted as prior approval supplements (21 CFR 601.12(f)(1)).

C. Requirements and Recommendations Applicable to NDA and BLA Supplements

The applicant should evaluate and address in the supplement the potential impact of shipping conditions, including holding and warehousing, necessary to import the MMA product on the safety and efficacy, identity, quality, purity, or potency of the MMA product, especially drug product stability, and reference supporting data in the NDA or BLA, or provide supporting data in the supplement.

The lots of MMA product produced under the approved supplement must meet applicable current good manufacturing practice requirements under the FD&C Act and FDA regulations. (See 21 U.S.C. 351(a)(2)(B); 21 CFR Parts 210-211; 21 CFR 314.50(d)(1); 21 CFR Parts 600-680; 21 CFR Part 4). Current good manufacturing practice records for the lots of the MMA product produced under the approved supplement must be established and retained as required by FDA regulations. (21 CFR Part 211, Subpart J; 21 CFR 600.12; 21 CFR Part 4, Subpart A; 21 CFR Part 820, Subpart M).

V. REGISTERING, LISTING, AND PROPOSING AN NDC FOR AN MMA PRODUCT

This section describes registration and listing of an MMA product as well as procedures for proposing an NDC for the MMA product. Drug products are identified and reported using a unique, three-segment NDC that serves as a unique product identifier for drugs. The segments of the NDC are the labeler code, the product code, and the package code. Generally, as described in further detail below, the request for the NDC is governed by 21 CFR 207.33, 207.35, and 207.37, and is required to be submitted as part of an electronic submission.

To obtain an NDC for an MMA product, the manufacturer should propose an NDC for the MMA product by following the procedures set forth in 21 CFR 207.33. Although a manufacturer may propose a change to either the labeler code or product code, as described above, an MMA product differs from the FDA-approved drug or FDA-licensed biological product only with regard to the labeling statement. For this reason, FDA recommends that a manufacturer seeking an NDC for an MMA product obtain a new labeler code. To avoid potential confusion between product packages with the same name, the change to the NDC for the MMA product should not be solely to the package code. To avoid confusion, if the MMA product label includes an NDC, the MMA product should bear only the NDC that FDA assigns to the MMA product. FDA recommends that the MMA product be listed under the marketing category for multi-market approved products, which FDA has added to the registration and listing system.

The procedures for registration and listing and proposing an NDC for MMA products are the same as the procedures for all FDA-approved drugs. Nothing in this guidance changes those procedures. Information about registration and listing, including a webinar, is available at www.fda.gov/edrls. Instructions for registration and listing are available at https://www.fda.gov/drugs/drug-registration-and-listing-system-drls-and-edrls/electronic-drug-registration-and-listing-instructions. For assistance with registration and listing of an MMA product, please email the eDRLS team at edrls@fda.hhs.gov.

VI. DEAR HEALTHCARE PROVIDER LETTER

In addition to the features recommended to be included on MMA product labeling to assist pharmacists and other healthcare providers in readily distinguishing an MMA product from other FDA-approved drugs, FDA recommends that manufacturers issue a Dear Healthcare Provider Letter (DHCP). DHCP letters are correspondence – often in the form of a mass mailing from the manufacturer or distributor of a human drug or from FDA – intended to alert physicians, pharmacists, and other health care providers about important new or updated information regarding a drug product. DHCP letters may also be distributed by email and are often made available on the Internet (e.g., on company websites or through patient advocacy groups). FDA recommends that a DHCP letter be issued upon approval of a supplement for an MMA product. The DHCP letter would help pharmacists and healthcare providers to distinguish an MMA product from a counterfeit or unapproved product. A DHCP letter will also help ensure that pharmacists and other healthcare providers can identify products and bill and submit claims information in an accurate manner. FDA has included a suggested template for a DHCP letter as Appendix A to this guidance.

VII. DRUG SUPPLY CHAIN SECURITY ACT

The DSCSA amended the FD&C Act and set forth, among other requirements, product tracing, product identifier, verification, and authorized trading partner[14] requirements for manufacturers,[15] repackagers, wholesale distributors, and dispensers to facilitate the tracing of certain prescription drugs through the pharmaceutical distribution supply chain. An MMA product offered for import that meets the DSCSA definition of a "product," like all DSCSA products, is subject to all applicable requirements of section 582 of the FD&C Act (21 U.S.C. 360eee-1).[16] For example, trading partners involved in transactions of DSCSA-covered MMA products are required to be authorized, which includes proper registration with FDA or licensure at the State or Federal level, as applicable.[17] Failure to comply with the requirements of section 582 of the FD&C Act is a prohibited act under section 301(t) of the FD&C Act (21 U.S.C. 331(t)) and subject to enforcement action under the FD&C Act.

An MMA product should be imported into the United States by the manufacturer of such product or by an authorized trading partner as defined in the DSCSA, when such importation is facilitated by the manufacturer under section 801(d)(1)(B) of the FD&C Act. This will help ensure that appropriate product safety and supply chain integrity safeguards are in place to reduce the possibility of counterfeit, substandard, or other unapproved products entering the closed U.S. supply chain.

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[14] *Authorized* is defined in section 581(2) of the FD&C Act (21 U.S.C. 360eee(2)). *Trading partner* is defined in section 581(23)(A) of the FD&C Act. Although third-party logistics providers are also considered trading partners under section 581(23)(B) of the FD&C Act, the requirements of section 582(a)-(e) are not applicable to them.

[15] *Manufacturer* is defined for the purposes of section 582 of the FD&C Act in section 581(10) of the FD&C Act and includes the NDA or BLA holder or co-licensed partner or affiliate of such holder.

[16] *Product* is defined in section 581(13) of the FD&C Act.

[17] See sections 582(b)(3), (c)(3), (d)(3), and (e)(3) of the FD&C Act.

A. Product Identification

Under the DSCSA, manufacturers are required to "affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction into commerce."[18] The manufacturer of a DSCSA-covered MMA product is required to affix or imprint the product identifier to each package and homogenous case of a product intended for marketing in the United States.[19] No transactions in interstate commerce may occur before the product identifier is affixed.[20] FDA recommends that manufacturers affix or imprint the required product identifier to the DSCSA-covered MMA product at the same time at which the FDA-approved label is applied. DSCSA-covered MMA products will not be considered "grandfathered" for purposes of the product identifier requirement, because they will be packaged after November 27, 2018.[21]

B. Product Tracing and Verification

Under section 582(b)(1), (c)(1), (d)(1), and (e)(1) of the FD&C Act, trading partners are required to provide the subsequent purchaser with product tracing information[22] for each transaction[23] involving a DSCSA-covered MMA product. For example, if the manufacturer transfers ownership of a DSCSA-covered MMA product to a wholesale distributor, the wholesale distributor generally shall not accept ownership of a product unless the manufacturer has, prior to or at the time of the transaction, provided the transaction history, transaction information, and a transaction statement for the product.[24]

Trading partners also are required to have verification systems in place for the DSCSA-covered MMA products to comply with the requirements under section 582(b)(4), (c)(4), (d)(4), and (e)(4) of the FD&C Act. These requirements include steps to handle suspect and illegitimate product.[25]

VIII. IMPORTATION OF MMA PRODUCTS

This section sets forth recommendations intended to assist importers of MMA products by facilitating an efficient and effective admissibility review. Following the procedures in this section will also assist FDA in determining that the importation is authorized and not, for example, a counterfeit.

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[18] See section 582(b)(2) of the FD&C Act. *Product Identifier* is defined in section 581(14) and includes the product's standardized numerical identifier, which is composed of the NDC and a unique alphanumeric serial number (see section 581(20)).
[19] See section 582(b)(2) of the FD&C Act.
[20] See section 582(b)(2) of the FD&C Act.
[21] See FDA Guidance for Industry *Grandfathering Policy for Packages and Homogenous Cases of Product Without a Product Identifier* (Sept. 2018). This guidance and other guidance documents on the DSCSA are available on FDA's website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[22] For purposes of this guidance, the term *product tracing information* refers to the transaction information, transaction history, and transaction statement defined in section 581(26), (25), and (27) of the FD&C Act.
[23] *Transaction* is defined in section 581(24) of the FD&C Act.
[24] See section 582(c)(1)(A) of the FD&C Act.
[25] *Suspect product* is defined in section 581(21), and *illegitimate product* is defined in section 581(8), of the FD&C Act.

A. Import Entries for MMA Products

To help FDA verify that a shipment that purports to contain an MMA product is one in which the manufacturer[26] has, in fact, authorized the drug to be marketed in the United States and has caused the drug to be labeled to be marketed in the United States, we strongly encourage the filing of an electronic entry in the Automated Commercial Environment (ACE). If a manufacturer plans to use or authorize another process for making entry of an MMA product other than ACE, such as a paper entry, we strongly encourage the manufacturer to inform FDA in advance. FDA's view is that international mail is not appropriate for the importation of MMA products.

ACE is currently the sole Electronic Data Interchange (EDI) system authorized by the U.S. Customs and Border Protection (CBP) to process electronic entry and entry summary filings for FDA-regulated products. Submitting complete, accurate information in ACE facilitates effective and efficient admissibility review by FDA. FDA regulations set forth the required data elements that must be submitted in an electronic entry in ACE, or any other EDI system authorized by CBP, for any entry that includes FDA-regulated products (21 CFR Part 1, Subpart D).[27]

At the time of filing entry in ACE, a filer must submit, among other elements, a Drug Listing Number, which is currently the NDC for drugs, including biological products and combination products, regulated by CDER (21 CFR 1.74). For drugs, biological products and combination products, regulated by CBER, the Drug Listing Number is not required. Although not required, FDA strongly encourages filers to submit the Drug Listing Number for CBER-regulated MMA products in ACE at the time of entry because this information will assist FDA's initial screening and further review of the entry, which can significantly increase the likelihood that the entry line will receive an automated "May Proceed" from FDA.

B. Manufacturer Authorization for MMA Products

As stated above, section 801(d)(1)(B) of the FD&C Act provides that, with limited exceptions:

> [N]o drug that is subject to section 503(b)(1) [of the FD&C Act] may be imported into the United States for commercial use if such drug is manufactured outside the United States, unless the manufacturer has authorized the drug to be marketed in the United States and has caused the drug to be labeled to be marketed in the United States.

Under this provision, any shipment of a purported MMA product that is offered for importation would be subject to refusal unless the manufacturer has authorized the MMA product to be marketed in the United States. It is essential that FDA be provided the information needed to confirm that each shipment of a purported MMA product offered for importation has been authorized for marketing in the United States by the manufacturer. To help ensure that a particular shipment is authorized, and to help mitigate the potential for counterfeiting, the manufacturer should provide information that is sufficient for FDA to verify that each shipment

[26] As noted in footnote 5, above, for purposes of this guidance, the manufacturer is the NDA or BLA holder for the MMA product.

[27] FDA published its final rule, "Submission of Food and Drug Administration Import Data in the Automated Commercial Environment," on November 29, 2016 (81 FR 85854), and the rule was effective December 29, 2016.

of an MMA product has, in fact, been authorized by the manufacturer to be marketed in the United States. This information is described in the following paragraph.

FDA strongly encourages manufacturers to submit a report via the Electronic Submissions Gateway (ESG) (or to an alternative transmission point identified by FDA) notifying the Agency of the importation of an MMA product 10 business days in advance of the first import entry of an MMA product covered by the report, which will facilitate FDA's timely admissibility review when the MMA product is offered for import. This report should include: the MMA product name, dosage form, and quantity of the MMA product; the name, address, and telephone number of the authorized importer; and any temporal or other limitations the manufacturer has placed on the authorized importation. For example, a report could authorize multiple shipments of an MMA product for a specified period of time. An updated report should be timely submitted by the manufacturer each time there is a change to the material information in the report; this updated report would be submitted before any additional imports affected by the changes are entered into ACE. Manufacturers who choose to submit this report must do so electronically in Portable Document Format (PDF) using the Electronic Common Technical Document (eCTD) format and the ESG (or to an alternative transmission point identified by FDA).[28] The report should be referenced and placed in Module 1. For further information regarding eCTD, please refer to FDA's website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

IX. OTHER REQUIREMENTS APPLICABLE TO AN MMA PRODUCT

An MMA product is subject to all relevant requirements of applicable statutes, including those implemented by FDA such as the FD&C Act and the PHS Act; applicable implementing regulations under those authorities; and other relevant statutes, including the Social Security Act, the Poison Prevention Packaging Act, and the Controlled Substances Act. The provisions implemented by FDA include, but are not limited to, provisions related to adulteration and misbranding, and requirements related to adverse event reporting (or postmarketing safety reporting for combination products under 21 CFR Part 4, Subpart B), recalls, and Risk Evaluation and Mitigation Strategies (REMS).

[28] FDA Guidance for Industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (Jan. 2019). For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Appendix A: Dear Healthcare Provider Letter

Dear Healthcare Provider
Month Year

IMPORTED PRODUCT FOLLOWING PROCEDURES IN: "Importation of Certain FDA-Approved Human Prescription Drugs, Including Biological Products, and Combination Products under Section 801(d)(1)(B) of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry" - MODEL LETTER

Subject: Importation of TRADENAME (*nonproprietary name for drugs/proper name for biological products)* (NDC #1, NDC #2): Availability of an FDA-approved *prescription drug/biological product/combination product* that was originally intended to be marketed in a foreign country and authorized for sale in that foreign country.

Dear Health Care Provider:

The purpose of this letter is to inform you that TRADENAME (NDC #1, NDC #2), an FDA-approved prescription *drug(s)/biological product(s)/combination product(s)* that was/were originally intended to be marketed in a foreign country and authorized for sale in that foreign country, will be available in the United States. SPONSOR is marketing TRADENAME (NDC #1, NDC #2) in the U.S. following the procedures in FDA guidance issued to describe a means for drug companies to offer lower cost versions of their *drugs/biological products/combination products* to Americans. In addition to marketing TRADENAME with NDC #1 and NDC #2, SPONSOR markets other lots of TRADENAME with NDC #10 and NDC #11 in the United States. TRADENAME marketed under NDC #10 and NDC #11 is also an FDA-approved prescription *drug*/*biological product/combination product*.

TRADENAME (NDC #1, NDC #2) will:

- have FDA-approved container and carton or package labeling;
- be identical in physical appearance to TRADENAME (NDC #10 , NDC #11), and
- be accompanied by other FDA-approved labeling (e.g., Prescribing Information, patient labeling). This labeling will include the proprietary name (if any) and the *nonproprietary name,* used for other lots of TRADENAME (NDC #10, NDC #11).

Lots of TRADENAME (NDC #1, NDC #2) will include certain features on the labels and labeling to distinguish these lots from other lots of TRADENAME (NDC #10, NDC #11). These features include a yellow (*or other contrasting color)* stripe printed within the top one-half of the container label and carton or package labeling.

The container label (or a peel-back label affixed to the container), the outside carton or package, and the Prescribing Information (in the HOW SUPPLIED/STORAGE AND HANDLING section or HOW SUPPLIED section) will include the statement (*or similar statement*), "Imported following the procedures recommended in FDA Guidance: see [insert current link to this guidance on FDA.gov]." This guidance titled, "Importation of Certain FDA-Approved

Human Prescription Drugs, Including Biological Products, and Combination Products under Section 801(d)(1)(B) of the Federal Food, Drug, and Cosmetic Act," provides more detailed information about this importation pathway, and is available on www.FDA.gov.

Reporting Adverse Events

Heath care providers and patients are encouraged to report adverse events that occur in patients taking TRADENAME to SPONSOR at 1-800-xxx-xxxx or to the FDA (Visit www.FDA.gov/medwatch, or call 1-800-FDA-1088).

You may also contact our medical information department at 1-800-xxx-xxxx if you have any questions about the information contained in this letter or the safe and effective use of TRADENAME.

This letter is not intended as a complete description of the benefits and risks related to the use of TRADENAME. Please refer to the enclosed prescribing information (and medication guide, *if there is a medication guide for the product*, or any other approved patient information).

Reporting Counterfeit Drugs

If you suspect that you may have a counterfeit drug, please report to FDA's MedWatch office (Visit www.FDA.gov/medwatch).

If you are aware of suspicious activity that may be associated with counterfeit prescription drugs, please contact FDA's Office of Criminal Investigations (OCI) (Send a report to OCI online at https://www.accessdata.fda.gov/scripts/email/oc/oci/contact.cfm or contact OCI headquarters in Rockville, Md.: 240-276-9500; Toll Free: 1-800-551-3989).

For additional information, please call Sponsor at 1-800-xxx-xxxx or visit www.tradename.com.

Sincerely,

Company Representative

Enclosure(s): TRADENAME Prescribing Information