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Drugs, Including Biological Products, under Section 801(d)(1)(B) of the Federal Food, Drug, and Cosmetic Act: Draft Guidance for Industry

***DRAFT GUIDANCE***

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**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Biologics Evaluation and Research (CBER)**
**Center for Drug Evaluation and Research (CDER)**
**Office of Regulatory Affairs (ORA)**

**December 2019**
Labeling
Pharmaceutical Quality/CMC

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Drugs, Including Biological Products, under Section 801(d)(1)(B) of the Federal Food, Drug, and Cosmetic Act: Draft Guidance for Industry

***This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

## I. Introduction

This guidance describes recommended procedures to obtain an additional National Drug Code (NDC) for an FDA-approved prescription drug that is 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).[1, 2] This guidance specifically addresses the importation of FDA-approved drugs that were also authorized for sale in a foreign country in which the drugs were originally intended to be marketed (hereinafter "multi-market approved product" or "MMA product)."[3]

In general, FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities.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

## II. Background

This guidance is intended to outline a potential pathway by which manufacturers could obtain an additional NDC for an FDA-approved drug that was originally intended to be marketed in a

[1] 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 approved under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262).

[2] This guidance addresses biologics license applications (BLAs) approved under either section 351(a) or section 351(k) of the PHS Act. This guidance is not intended to address certain biological products, such as blood and blood products, 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 requirements to obtain a U.S. license.

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

foreign country and was 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 additional NDC, 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 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 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.[4] 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 or misbranded.

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 new drug application (NDA) or biologics license application (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 additional 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.[5]

# III. Description and Labeling of an MMA Product

## A. Description

This guidance specifically addresses the importation of FDA-approved drugs that were 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 biological product that:

- was originally manufactured outside the United States and authorized for marketing by another country's regulatory authority;

[4] 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.

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

- is the subject of a supplement to an NDA or a BLA, including all the information described in section IV.A. or B.;
- is imported into the United States and is authorized by the manufacturer under section 801(d)(1)(B) of the FD&C Act to be marketed in the United States;
- continues to meet the quality standards for marketing in its originally intended market;[6] and
- differs from the FDA-approved drug or FDA-licensed biological product only with regard to the labeling statement described in section III.B.

## B. Labeling

Under the procedures described in this guidance, an MMA product, like any FDA-approved prescription drug, must be accompanied by the FDA-approved labeling (e.g., Prescribing Information). (See, e.g., 21 U.S.C. § 352(f); 21 CFR 201.5; 21 CFR 201.100(c)). This means that if a product is marketed outside the United States with a trade name that differs from that of the U.S.-approved drug, the MMA product labeling must match the FDA-approved labeling, including the proprietary name (if any) used in that approved labeling. (See, e.g., 21 CFR 201.57(a)(2)). In addition, FDA recommends that the labeling on or within the package (except for FDA-approved patient labeling) from which the MMA product is dispensed include a statement to differentiate the drug from other drugs that are not the subject of this guidance (if finalized).

To help avoid potential confusion between product packages with the same name, this statement should be included after the PATIENT COUNSELING INFORMATION section for products subject to 21 CFR 201.56(d) and 201.57, or after the HOW SUPPLIED section for products subject to 21 CFR 201.56(e) and 201.80. The statement also should be included on the immediate container and outside package to help pharmacists distinguish an MMA product when selecting the product on the pharmacy shelf. The statement 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).[7]

# IV. Submission of Supplement for an MMA Product

This section describes the process by which the holder of an approved application may obtain marketing approval of the 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. Generally, FDA recommends that an applicant seeking to

[6] A product's failure to meet the quality standards of the regulatory authority under which it was originally intended for marketing may suggest the existence of manufacturing process control issues in the production of that product.

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

market an MMA product under an NDA or a BLA submit a labeling supplement under 21 CFR 314.70 or 601.12(f), respectively, because 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).

The supplement should include an attestation to demonstrate that the MMA product is the FDA-approved drug product, 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.

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 the 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, meet 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), and route(s) of administration described in the NDA. The attestation also should include a statement 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 drug substances, 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 is manufactured, packaged, labeled, and tested at the facility(ies) approved in the NDA, including specific site(s) and production lines as appropriate. 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 executed 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.[8] The supplement should include information to demonstrate that the 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 limited exception of the labeling statement 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. (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 biological products licensed under section 351 of the PHS Act, 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 and is manufactured in accordance with the FDA-approved BLA, with the exception of the limited labeling differences discussed in this guidance. The attestation should also include a statement 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 MMA product should conform 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, and tested in the FDA-licensed biological product's facilities using the same manufacturing line(s) that are used to manufacture the FDA-licensed biological product.

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

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 executed COAs 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.

### 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 identity, quality, purity, or potency of the drug 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 314.50(d)(1); 21 CFR parts 210-211; 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, and 21 CFR 600.12).

## 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 additional NDC for the MMA product. Drug products are identified and reported using a unique, three-segment number that serves as a universal 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 additional 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. To avoid potential confusion between product packages with the same name, the change to the NDC for the MMA product should not be solely with the package code. FDA recommends that the MMA product be listed under the marketing category for multi-market approved products, which FDA intends to add to the registration and listing system.

The procedures for registration and listing, and proposing an additional 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. 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[9] requirements for manufacturers,[10] 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" is subject to all applicable requirements of section 582 of the FD&C Act (21 U.S.C. 360eee-1).[11] 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.[12] 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 to 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.

## 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."[13] The manufacturer of a DSCSA-covered MMA product is required to affix or

[9] *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.
[10] *Manufacturer* is defined 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.
[11] *Product* is defined in section 581(13) of the FD&C Act.
[12] See sections 582(b)(3), (c)(3), (d)(3), and (e)(3) of the FD&C Act.
[13] 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)).

imprint the product identifier to each package and homogenous case of a product intended for marketing in the United States.[14] FDA recommends that manufacturers affix or imprint the required product identifier to the DSCSA-covered MMA product at the 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.[15]

## 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[16] for each transaction[17] 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.[18]

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.[19]

# VII. 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 ensuring the importation is authorized and not, for example, a counterfeit.

## 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 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

[14] See section 582(b)(2) of the FD&C Act.

[15] See FDA Guidance for Industry *Grandfathering Policy for Packages and Homogenous Cases of Product Without a Product Identifier* (Sept. 2018).

[16] 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.

[17] *Transaction* is defined in section 581(24) of the FD&C Act.

[18] See section 582(c)(1)(A) of the FD&C Act.

[19] *Suspect product* is defined in section 581(21), and *illegitimate product* is defined in section 581(8), of the FD&C Act.

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).[20]

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 and biological products regulated by CDER (21 CFR 1.74). For drugs regulated by CBER, the Drug Listing Number is not required. Although not required, FDA strongly encourages filers to submit the Drug Listing Number for such MMA products in ACE at the time of entry because this information will assist FDA in expediting the 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 drug to be marketed in the United States. It is essential that FDA is 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 its manufacturer. To 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 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) 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 drug is offered for import. This report should include: the drug name, dosage form, and quantity of the drug; the name, address, and telephone

[20] 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), which was effective December 29, 2016.

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.[21] The report should be referenced and placed in Module 1. For further information regarding eCTD, please refer to the Web site at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

# VIII. 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 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, recalls, and Risk Evaluation and Mitigation Strategies (REMS).

[21] FDA Guidance for Industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (Jan. 2019).