Pre-Launch Activities Importation Requests (PLAIR)

Guidance for Industry

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

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Additional copies are available from:
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Contains Nonbinding Recommendations

Pre-Launch Activities Importation Requests (PLAIR) Guidance for Industry[1]

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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance finalizes the July 2013 draft guidance *Pre-Launch Activities Importation Requests (PLAIR)*, which describes the FDA's policy regarding requests for the importation of unapproved finished dosage form drug products by an applicant preparing the product for U.S. market launch based on anticipated approval of a pending new drug application (NDA) or abbreviated new drug application (ANDA).[2] This guidance also applies to unapproved biologics licensing applications (BLAs) regulated by the Center for Drug Evaluation and Research (CDER), and unapproved combination products assigned to CDER (21 CFR part 3) for which NDA, ANDA, or BLA approval is anticipated. Moreover, this guidance describes the procedures for making requests for importation of unapproved finished dosage form drug products before final approval of the application and the factors that FDA will consider in granting such requests.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Historically, when applicants sought to import unapproved finished dosage form drug products in preparation for market launch, FDA considered such requests, referred to as Pre-Launch Activities Importation Requests (PLAIRs), on a case-by-case basis. In July 2013, FDA issued a draft guidance announcing the Agency's approach for overseeing the import of some unapproved

[1] This guidance has been prepared by the Office of Compliance, Center for Drug Evaluation and Research (CDER), in cooperation with the Office of Enforcement and Import Operations in the Office of Regulatory Affairs (ORA) at the Food and Drug Administration.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

finished dosage form drug products regulated by CDER prior to their approval to facilitate the availability of those products to patients upon approval. This guidance adopts most elements of the PLAIR program announced in the July 2013 draft guidance, updates the information that should be submitted to FDA in a PLAIR, describes when and how a PLAIR can be submitted, and explains the circumstances under which the Agency intends to grant a PLAIR.

III. DISCUSSION

Section 505(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(a)) prohibits the introduction or delivery for introduction into interstate commerce of a new drug "unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug." Section 801(a)(3) of the FD&C Act (21 U.S.C. 381(a)(3)) states that a drug being imported or offered for import is subject to refusal of admission into the United States if, among other things, it appears that it violates section 505 of the FD&C Act. If a drug is subject to refusal of admission under section 801(a)(3) because it appears to violate section 505 of the FD&C Act, FDA issues a notice of the detention and the opportunity to introduce testimony to the owner or consignee of the shipment. The owner or consignee may request an informal hearing to introduce testimony that the drug can be imported. Under section 801(b) of the FD&C Act, if a drug is detained under 801(a)(3), the owner or consignee may also request permission to recondition the drug to bring it into compliance. FDA has issued regulations on reconditioning found at 21 CFR 1.95-1.99.

An applicant[3] who has a pending NDA, ANDA, or CDER-regulated BLA nearing an FDA application decision (timeframes discussed below) can submit a PLAIR to FDA seeking permission to import an unapproved finished dosage form drug product for reconditioning in the form of approval. As a benefit of PLAIR, FDA reviews the reconditioning request prior to the drug's arrival at the port of entry. As a result, applicants whose PLAIR requests have been granted need not complete a Form FDA 766 requesting reconditioning, which is the process described in the Regulatory Procedures Manual, Chapter 9: Imports Operations and Actions[4] for requesting reconditioning.

The PLAIR submission should include a statement that the owner or consignee has requested to recondition the drug by obtaining FDA approval of the pending application. Once the drug arrives at the port of entry, FDA will issue a "Notice of FDA Action-Detained" for any product associated with a granted PLAIR. We intend to detain the product for up to 6 months pending a decision on the underlying application. If FDA approves the underlying NDA, ANDA, or BLA, the Agency intends to issue a "Release after Detention." If FDA refuses to approve the application or 6 months otherwise elapse without FDA approval, FDA may determine that the product is subject to refusal and may issue a "Notice of FDA Action-Refusal of Admission."[5]

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[3] For purposes of this guidance, an *applicant* is any person who submits an NDA, ANDA, or a CDER-regulated BLA to request FDA approval of a new drug or biological product.

[4] See https://www.fda.gov/media/71776/download.

[5] We believe that 6 months is generally a reasonable limit for detentions under PLAIR because after 6 months, the Agency's goal date for most reviews of applications will have elapsed. If applicants believe that FDA should extend the detention for more than 6 months, they may contact FDA.

Applicants are not required to submit a PLAIR. FDA's granting of a PLAIR does not represent an implicit or explicit statement of the approvability of the NDA, ANDA, or CDER-regulated BLA. Rather, PLAIR facilitates the process for importing unapproved finished dosage form products to prepare for market launch based on anticipated approval of the pending application. This guidance describes all the information FDA needs to evaluate PLAIR requests.

A. Submitting a PLAIR

1. Which Drug Products Does the PLAIR Program Cover?

The PLAIR program covers finished dosage form drug products that are the subject of a pending NDA, ANDA, or CDER-regulated BLA.[6] The unapproved finished dosage form drug products should either:

- Call for minimal further processing, such as final packaging and/or labeling; or
- Be in final packaged form.

2. What Should Be Included in a PLAIR?

a. The drug product name and how supplied (from product labeling per 21 CFR 201.56 and 201.80).

b. The name of the CDER Office of New Drugs or Office of Generic Drugs regulatory project manager assigned to the pending application.

c. The National Drug Code (NDC) number, if assigned.

d. The name, address, registration number,[7] and telephone number of the foreign manufacturer of the finished dosage form drug product.

e. The name, address, registration number, and telephone number of the U.S. consignee.

f. The application number for the finished dosage form drug product pending FDA approval.

[6] Consistent with our resources, FDA does not intend to consider PLAIR requests for drug products that are the subject of a supplement or other change to an approved application. However, sponsors of such products may choose to offer those products for import. Since they are unapproved drug products, the products are subject to detention. FDA will review such entries and make admissibility determinations in accordance with FDA-administered statutes and regulations.

[7] Note that FDA will assess whether foreign drug establishments are in compliance with applicable registration requirements in section 510(i) of the FD&C Act (21 U.S.C. 360(i)) and 21 CFR part 207.

g. A letter from FDA officially documenting the user fee goal date.[8]

h. The precise quantities to be imported.

i. The name, address, facility identification number (such as a Data Universal Number or DUNS[9]), and telephone number of any facility where the finished dosage form drug product in final packaged form will be stored pending approval.[10]

j. When the finished dosage form drug product is imported for minimal further processing, information regarding the facility where minimal further processing activities will occur, including (1) the name, address, and registration number of the facility; and (2) a description of the further processing activities. This facility should be identified in the pending application.

k. A letter signed by an authorized representative of the applicant stating the following:

   i. The applicant's acknowledgment that the product is an unapproved new drug;

   ii. That the PLAIR represents the applicant's request to recondition the product, under section 801(b) of the FD&C Act and 21 CFR 1.95, by obtaining product approval within 6 months;

   iii. For an unapproved finished dosage form drug product that calls for minimal further processing, that the unapproved finished dosage form drug product will be delivered to a facility identified in the finished dosage form drug product's pending application to permit further processing. Following completion of those activities, the product will remain subject to the terms and conditions of the U.S. Customs and Border Protection (CBP) entry bond that covers the specific shipment.

   For an unapproved finished dosage form drug product in final packaged form that does not call for further processing, that the drug product should be delivered to a *single* facility used for warehousing. The product will remain subject to the terms and conditions of the CBP entry bond that covers the specific shipment;

[8] As part of the reauthorization of the Prescription Drug User Fee Act and the Generic Drug User Fee Amendments, FDA commits to certain performance goals (see FDA's User Fee Programs web page, available at https://www.fda.gov/industry/fda-user-fee-programs).

[9] Dun & Bradstreet D-U-N-S Number is a unique nine-digit number used around the world to identify and access information on businesses (see https://www.dnb.com/duns-number.html).

[10] For entities that conduct activities of a *third-party logistics provider*, as defined in section 581(22) of the FD&C Act, please see the requirements of reporting and licensure requirements under section 584 of the FD&C Act (21 U.S.C. 360eee-3).

iv. That the facility used for warehousing complies with any applicable current good manufacturing practices (CGMP) or if applicable, other federal or state requirements.[11]

v. That the applicant understands that the unapproved finished dosage form drug product must be exported or destroyed within 90 days of the date of any notice of refusal, if refused admission.

3. When Should a PLAIR Be Submitted?

The PLAIR should be submitted at least 30 days prior to the proposed entry date of the shipment to allow time to process the submission. In addition, we provide the following timeframes:

- For PLAIR-eligible ANDAs, NDAs, and CDER-regulated BLAs subject to standard review: The PLAIR should be submitted no more than 60 days before the user fee goal date.

- For PLAIR-eligible NDAs and CDER-regulated BLAs subject to 6-month (priority) review,[12] the PLAIR should be submitted up to 120 days before the user fee goal date.

- For PLAIR-eligible ANDAs subject to priority review,[13] the PLAIR should be submitted up to 80 days before the user fee goal date.

These recommended timeframes will help ensure that PLAIR requests are processed in time for FDA to review the underlying application.

4. How Should a PLAIR Be Submitted?

The PLAIR submission should be on the applicant's letterhead and submitted by email to CDER-OC-PLAIR@fda.hhs.gov[14] in a file compatible with Portable Document Format (PDF). The subject line of the submission should include the application number, drug product name and strength(s). Consistent with our resources, FDA intends to accept one PLAIR submission per NDA, ANDA, or BLA.

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[11] If third-party logistics providers are used, they shall have a valid license under state law or section 584(a)(1) of the FD&C Act in accordance with sections 582(a)(7). They should also comply with the licensure reporting requirements under section 584(b) of the FD&C Act to be considered as authorized.

[12] FDA assigns priority review designation to applications for new drugs or biological products that are to treat serious conditions and, if approved, would provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions. See FDA's guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014). In addition, the FD&C Act provides for other expedited programs for certain types of applications. See 21 U.S.C. 356 and FDA's guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014).

[13] Information on ANDAs eligible for priority or expedited review is provided in CDER's Manual of Policy and Procedures (MAPP) 5240.3 Prioritization of the Review of Original ANDAs, Amendments and Supplements. See https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-guidances-and-mapps.

[14] If, and when, an electronic submissions portal becomes available, FDA will post instructions for use on our website.

5. What Action Will FDA Take on a PLAIR?

Once a complete PLAIR is submitted to FDA, the CDER Office of Drug Security, Integrity and Response (ODSIR), Division of Global Drug Distribution and Policy (DGDDP), will confirm receipt of the submission. CDER will review the submission and assess, among other things, the foreign facility's inspection history and conformity with applicable CGMP (e.g., 21 CFR parts 210 and 211). Following this review, DGDDP will notify the applicant whether the PLAIR has been granted or denied.

If any changes to the PLAIR are proposed after FDA has granted the original PLAIR submission, an amended PLAIR should be submitted to FDA. The firm may make the changes on the initial PLAIR. However, the firm should explain all changes made and identify the document as an "amendment" to differentiate it from the initial PLAIR request. After review, DGDDP will notify the applicant whether it has granted the amendment.

B. Importation Procedures Under a PLAIR

Upon receiving a granted PLAIR, the importer may provide a copy of the granted PLAIR to the Office of Regulatory Affairs (ORA) Import Division where the product is imported. The importer should provide an affirmation of compliance indicating the product is covered under a granted PLAIR as well as the associated drug application number in the Automated Commercial Environment (ACE).[15] FDA will consider this action to mean that the owner or consignee is requesting to recondition the drug under section 801(b) of the FD&C Act and 21 CFR 1.95. We also consider that the owner or consignee has opted not to request a hearing on refusal of admission under section 801(a) of the FD&C Act and 21 CFR 1.94. For PLAIRs that FDA grants, FDA intends to detain the product as an unapproved new drug and to authorize the drug's reconditioning in the manner and under the conditions set forth in the granted PLAIR. If FDA approves the products in the application (NDA, ANDA, or CDER-regulated BLA) within 6 months of the date of entry of the shipment made under the PLAIR, then the Agency intends to issue a "Release after Detention" for the drug product.

If FDA refuses to approve the application or 6 months otherwise elapse without FDA approval, FDA may determine that the product is subject to refusal. If FDA refuses admission into the United States under section 801(a)(3) of the FD&C Act, the finished dosage form drug product must be exported or destroyed within 90 days of the refusal.

C. Post-NDA, ANDA, or CDER-Regulated BLA Approval

Upon receiving notice from FDA that a drug product application is approved, the applicant should immediately send a copy of the approval letter to the ORA Import Division where the product was detained and CDER-OC-PLAIR@fda.hhs.gov. The applicant should notify FDA of

[15] For general information about importation and ACE, see FDA's web pages https://www.fda.gov/industry/import-systems/automated-commercial-environmentinternational-trade-data-system-aceitds and https://www.fda.gov/industry/entry-process/entry-submission-process.

any deviation of the drug product detained under a PLAIR from the provisions in the approved drug application.

In the past, the Agency has encountered instances in which drug products that had been warehoused subject to a pending drug approval did not conform with late changes made to the approved drug product labeling or instances in which the application did not receive FDA approval. Under these circumstances, such products may be misbranded under section 502 of the FD&C Act (21 U.S.C. 352) and/or constitute unapproved new drugs under section 505 of the FD&C Act, because it may differ from the approval of the NDA, ANDA, or BLA. Introduction or delivery for introduction into interstate commerce of any misbranded drug or any article in violation of section 505 of the FD&C Act is prohibited, and such products are subject to refusal of admission.

Applicants must list their drug product(s) in accordance with section 510(j) of the FD&C Act.

IV. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521).

The collections of information pertaining to FDA's Pre-Launch Activities Importation Requests have been approved under OMB control number 0910-0046.

The time required to complete this information collection is estimated to average 16 hours for the first submission, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. We expect the subsequent submissions to take less than 16 hours.

Send comments regarding this burden estimate or suggestions for reducing this burden to the Office of Regulatory Policy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6282, Silver Spring, MD 20993-0002, and include Docket No. FDA-2013-D-0836 (see the announcement of the guidance published in the *Federal Register* on March 2, 2022).

The guidance also refers to previously approved collections of information. The collections of information in 21 CFR part 314 relating to new drug applications and abbreviated new drug applications have been approved under OMB control number 0910-0001; the collections of information in part 601 relating to biologics license applications have been approved under OMB control number 0910-0338; the collections of information in 21 CFR part 207 relating to domestic and foreign facility registration, including assignment of a national drug code, have been approved under OMB control number 0910-0045; and the collections of information in parts 210 and 211 pertaining to current good manufacturing practice requirements have been approved under OMB control number 0910-0139.

V. CONTACTS

For questions regarding this guidance or a PLAIR please contact:

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