Guidance for Industry

Pre-Launch Activities Importation Requests (PLAIR)

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Alternatively, electronic comments may be submitted to http://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Marybet Lopez at CDER, 301-796-3130.

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

July 2013
Procedural

Guidance for Industry

Pre-Launch Activities Importation Requests (PLAIR)

Additional copies are available from:
Office of Communication
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

July 2013
Procedural

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 1

III. DISCUSSION 2

A. Submitting a PLAIR 2

B. Importation Procedures Under a PLAIR 5

C. Post-NDA, ANDA, or BLA Approval 6

IV. CONTACTS 6

Guidance for Industry[1]

Pre-Launch Activities Importation Requests (PLAIR)

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance describes the Food and Drug Administration (FDA or the Agency) policy regarding requests for the importation of unapproved finished dosage form drug products by an applicant preparing the product for market launch, based on anticipated approval of a pending new drug application (NDA) or an abbreviated new drug application (ANDA). This guidance also applies to biologics licensing applications (BLA) regulated by the Center for Drug Evaluation and Research (CDER). This guidance further describes the procedures for making these requests and the factors that FDA will consider in granting such requests.

FDA's guidance documents, including this 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

Historically, when applicants sought to import unapproved finished dosage form drug products in preparation for market launch, FDA considered such requests, informally referred to as Pre-Launch Activities Importation Requests (PLAIRs), on a case-by-case basis. FDA has decided to create a more formal program, and this guidance outlines what information should be submitted to FDA in a PLAIR, when and how a PLAIR can be submitted, and the circumstances under which the Agency intends to grant a PLAIR.

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

III. DISCUSSION

Section 505(a) of the Federal Food, Drug, and Cosmetic Act (the 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 FDA has determined that an article of drug is subject to refusal of admission under section 801(a), FDA gives notice of this to the owner or consignee (often referred to as detaining the product). The owner or consignee then has an opportunity to introduce evidence regarding the admissibility of the drug. 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, such as to bring it into compliance.

An applicant who has an NDA, an ANDA, or a BLA pending that is nearing an FDA application decision can submit a PLAIR request to FDA regarding the importation of the unapproved finished dosage form drug product that is the subject of the application to prepare the product for market launch. If FDA grants the PLAIR request, when the product is then offered for import, FDA intends to detain the unapproved finished dosage form drug product. FDA will, however, regard the PLAIR request to mean that the owner or consignee has requested to recondition the drug by obtaining FDA approval of the pending application, as specified in the PLAIR request FDA has granted. FDA will thus detain the drug for up to 6 months pending a decision on the underlying application. The Agency will release the drug product when and if FDA approves the underlying NDA, ANDA, or BLA within 6 months and the conditions of the PLAIR are otherwise met.

A. Submitting a PLAIR

1. When Is a Drug Product Eligible for a PLAIR?

This guidance applies only to finished dosage form drug products. 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.

Prior to submitting a PLAIR:

- Firm(s) not exempt under section 510(g) of the FD&C Act (21 U.S.C. 360(g)) or subpart B of 21 CFR part 207 must register with FDA as required by section 510(i) of the FD&C Act.

2. What Should Be Included in a PLAIR?

(a) The drug product name (trade and established) and how supplied (complete **product description**).

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

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

(d) The name, address, registration number, 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 that is pending approval by FDA.

(g) The name, address, registration number, and telephone number of the warehouse or the distribution facility controlled by or under contract with the applicant where the finished dosage form drug product in final packaged form will be stored pending approval. This facility should be identified in the pending application.

(h) When finished dosage form drug product in bulk is imported for minimal further processing, information regarding the facility where minimal further processing activities will occur, including (1) the name and address of the facility, (2) a description of the further processing activities, (3) information about where the unapproved finished dosage form drug product in final packaged form will be stored pending approval, and (4) the registration number. This facility should be identified in the pending application.

(i) A letter signed by an authorized representative of the applicant certifying the following:

i. The applicant's acknowledgment that the product is an unapproved new drug.
ii. That the PLAIR represents the applicant's advance 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 bulk 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 at the facility where the processing occurred or be transferred to a single site consisting of a warehouse or a distribution facility controlled by or under contract with the applicant
- Remain under quarantine pending final approval of the application
- Remain subject to the terms and conditions of the U.S. Customs and Border Protection (CBP) entry bond that covers the specific shipment

iv. For an unapproved finished dosage form drug product in final packaged form that does not call for further processing, that the drug product will be delivered to a single site consisting of a warehouse or a distribution facility controlled by or under contract with the applicant. The product will:

- Remain under quarantine pending final approval of the application
- Remain subject to the terms and conditions of the CBP entry bond that covers the specific shipment

v. That the warehouse/distribution facility controlled by or under contract with the applicant complies with applicable current good manufacturing practice (CGMP), including proper storage conditions and appropriate temperature and humidity controls as required by 21 CFR 211.42 and 211.46.

vi. That the certifying firm understands that the unapproved finished dosage form drug product should be exported or destroyed within 90 days if it is refused admission.

3. When Should a PLAIR Be Submitted?

The following time frames apply (Please note: the PLAIR should be submitted at least 30 days prior to the proposed arrival date of the shipment to allow time to process the request):

- For NDAs and BLAs: The applicant should submit a PLAIR no more than 60 days before the user fee goal date for completion of the review of the pending application for approval. For requests submitted more than 60 days before the user fee goal date,[2] an applicant should explain the reason for the early request.

- For ANDAs: A PLAIR should be submitted no more than 60 days prior to expecting full approval or, for ANDAs submitted after October 1, 2014, 60 days before the user fee goal date for completion of the review of the pending application for approval.

[2] As part of the reauthorization of the Prescription Drug User Fee Act (PDUFA V), FDA committed to certain performance goals available on the Internet at http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf.

For requests submitted more than 60 days before the user feel goal date,[3] an applicant should explain the reason for the early request.

4. How Should a PLAIR Be Submitted?

Applicants should submit a PLAIR on the firm's letterhead by e-mail only, in a file compatible with Portable Document Format (PDF), to CDER-OC-PLAIR@fda.hhs.gov. The applicant should include in subject line the application number and drug product name. Before submitting a PLAIR, applicants should ensure that they include the actual quantities they plan to import. One PLAIR should be submitted for each application number. The complete PLAIR should be submitted by the applicant within the time frames noted in section III.A.3 of this guidance.

5. What Action Will FDA Take on a PLAIR?

Once a complete PLAIR is submitted to CDER-OC-PLAIR@fda.hhs.gov, an e-mail confirmation of receipt will be sent. CDER then will review the submission and determine, among other things, whether the responsible foreign facility has a satisfactory inspection history and is in substantial conformity with applicable CGMP (21 CFR parts 210 and 211). Following FDA's review, the CDER Office of Drug Security, Integrity and Recalls (ODSIR), Division of Import Operations and Recalls, will notify the applicant whether the PLAIR has been granted. The notification will be communicated by e-mail to the applicant and the Office of Regulatory Affairs (ORA).

If any changes are proposed after FDA has granted the original PLAIR submission, an amended PLAIR should be submitted to CDER-OC-PLAIR@fda.hhs.gov. After review, CDER ODSIR will notify the applicant and ORA whether it has granted any amendments to the PLAIR.

B. Importation Procedures Under a PLAIR

When an unapproved finished dosage form drug product is imported or offered for import under a PLAIR that FDA has granted and the importer provides at entry an affirmation of compliance with the PLAIR and the associated application number, FDA will consider this 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, and that the owner or consignee has opted not to request a hearing on refusal of admission under section 801(b) of the FD&C Act and 21 CFR 1.94. 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 PLAIR. If FDA approves the application (NDA, ANDA, or BLA) within 6 months of the date of entry of the initial shipment made under the PLAIR and the conditions of the PLAIR are otherwise met, then the Agency will release the drug product. FDA intends to refuse admission into the United States under section 801(a)(3) of the FD&C Act if the Agency does not approve the sponsor's application, if 6 months have passed since the entry date of the initial shipment under the PLAIR, or if the conditions of the PLAIR are otherwise not met. If FDA refuses admission into the United States, under section 801(a)(3)

[3] As part of the Generic Drug User Fee Act (GDUFA), FDA committed to certain performance goals available on the Internet at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf.

of the FD&C Act, the finished dosage form drug product should be exported or destroyed within 90 days of the refusal.

C. Post-NDA, -ANDA, or -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 by e-mail to the FDA district office and to DIOP Plair@fda.hhs.gov. FDA will use the PLAIR submission in determining whether the finished dosage form drug product that was imported under a PLAIR conforms to the approved application. CDER's ODSIR should be notified of 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. 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.

Please note: Firms must list their drug product(s), as required by section 510(j) of the FD&C Act, prior to commercial distribution.

IV. CONTACTS

For questions regarding this guidance please contact:

CDER Office of Compliance:
Office of Drug Security, Integrity and Recalls (ODSIR)
Division of Import Operations and Recalls
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
FAX: 301-847-8747
Main number: 301-796-3130
E-mail: CDER-OC-PLAIR@fda.hhs.gov

ORA DIO:
Division of Import Operations (HFC-170)
Office of Regional Operations
Food and Drug Administration
12420 Parklawn Drive, Rm. 3109
Rockville, MD 20857
Main number: 301-796-0356

260 Fax: 301-827-4086
261 E-mail: DIOP Plair@fda.hhs.gov