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ALERT

In Case You Missed It: Takeaways from Final Guidance for Submitting Pre-Launch Activities Importation (PLAIR) Requests to FDA for Drug Products Prior to Anticipated Approval

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The U.S. Food and Drug Administration (FDA or Agency) recently announced the final guidance titled "Pre-Launch Activities Importation Requests (PLAIR)" (Final Guidance). The Final Guidance outlines FDA's policy for the importation of unapproved finished dosage form drug products an applicant is preparing for a U.S. market launch based on anticipated approval of a pending new drug application (NDA), an abbreviated new drug application (ANDA), or a biologics licensing application regulated by FDA's Center for Drug Evaluation and Research (CDER). The guidance describes the procedures for making such a request to FDA before final approval of the application and provides factors the Agency will consider in granting such requests. FDA offers the following procedural information in the Final Guidance: (1) what information should be submitted to FDA in a PLAIR; (2) when and how to submit a PLAIR; and (3) the circumstances under which the Agency intends to grant a PLAIR.

The Final Guidance finalizes and updates the draft guidance of the same title issued on July 24, 2013. Below please find a summary of the major provisions in the Final Guidance, as well as our takeaways to assist industry in preparing and submitting PLAIRs.

MAJOR PROVISIONS

Purpose of a PLAIR

Practice Areas

Food & Drug

Pharmaceuticals, Biologics, and Life Sciences

In finalizing this guidance, FDA hopes to assist those applicants that want to make drug products available to patients upon approval. Through this process, applicants can cut down on the time it takes to deliver an imported new drug to patients that require it when the application is likely to be approved by the Agency. An applicant that is granted a PLAIR will be allowed to present their drug product for import into the United States, where it will be detained by FDA until the underlying application is approved or denied. The applicant must deliver the detained drug to a facility listed in the pending application and maintain it there pending approval. Importantly, those applicants whose PLAIR requests are granted do not need to complete a Form FDA-766 to request reconditioning of their product upon approval. Applicants are not required to submit a PLAIR, but FDA believes this approach will facilitate the importation process for those who wish to do so.

The "When" of a PLAIR

FDA provided the timeframes below for when an applicant should submit a PLAIR.

Timeframes for PLAIR Submissions Based on Submission Type

Submission Type

Minimum Timeframe

Maximum Timeframe

NDAs, ANDAs, and CDER-regulated BLAs subject to standard review

At least 30 days prior to the proposed entry date of the shipment

No more than 60 days before user fee goal date

NDAs and CDER-regulated BLAs subject to priority (6-month) review

Up to 120 days before the user fee goal date

ANDAs subject to priority (6-month) review

Up to 80 days before the user fee goal date

The "What" of a PLAIR

The following information should be included in a PLAIR:

1. The drug product name and how it is supplied.
2. The name of the regulatory project manager assigned to the pending application. This project manager will be from the CDER Office of New Drugs or Office of Generic Drugs.

3. The National Drug Code (NDC) number if one has been assigned.
4. The name, address, registration number, and telephone number of the foreign manufacturer of the finished dosage form drug product.
5. The name, address, registration number, and telephone number of the U.S. consignee.
6. The application number for the drug product that is pending FDA approval.
7. A letter from FDA documenting the user fee goal date.
8. The precise quantities to be imported.
9. The name, address, facility identification number, and telephone number of any facility where the finished dosage form drug product in final packaged form will be stored pending approval.
10. If applicable, information regarding the facility where minimal processing activities of the drug product will occur, including (a) the name, address, and registration number of the facility; and (b) a description of the further processing activities. This facility should also be identified in the pending application.

Applicants are also required to submit a signed letter stating the following:

1. Applicant's acknowledgement that the product is an unapproved new drug;
2. The PLAIR represents the applicant's request to recondition the product by obtaining product approval within 6 months;
3. The unapproved finished dosage form drug product will be delivered to a facility identified in the product's pending application for warehousing or further processing. For products in final packaged form that do not require further processing, FDA indicated the drug should be delivered to a *single* facility for warehousing;
4. The facility used for warehousing will comply with applicable current good manufacturing practices (CGMP) or, if applicable, other federal or state requirements;[1] and
5. The applicant understands the drug product must be exported or destroyed within 90 days if FDA issues a "Notice of FDA Action-Refusal of Admission" because FDA did not approve the application or 6 months otherwise elapsed without FDA approval.

The "How" of a PLAIR

FDA requests that PLAIRs be submitted via email to CDER-OC-PLAIR@fda.hhs.gov in PDF format. The subject line of the message should include the application number, drug product name, and drug strength(s).

FDA Response to a PLAIR

Upon submission to FDA, CDER will confirm receipt of the PLAIR. CDER will then review the submission and notify the applicant whether the request has been granted or denied. FDA does not commit to any specific timeline in the Final Guidance. However, the maximum timeframes for submission types may give a hint to FDA

expected response times.

If an applicant wants to make changes to a PLAIR after it has been granted, FDA requests the applicant submit an amended PLAIR to the Agency. The applicant may resubmit the original PLAIR with the proposed changes, but the applicant should identify the document as an "amendment" to the initial submission. FDA requests the applicant provide an explanation for all changes made in the updated submission.

Approval Process

Once a PLAIR has been granted by FDA, the importer (applicant) should provide a copy of the granted PLAIR to the Office of Regulatory Affairs (ORA) Import Division at the place of entry. This should not be misconstrued to mean the product has been approved for market sale by FDA. Rather, FDA will grant a PLAIR to indicate the Agency's intention to detain the product as an unapproved new drug and authorize the drug's reconditioning according to the PLAIR. The importer should also provide an affirmation of compliance indicating that the product is covered by a granted PLAIR and the associated drug application number to the ORA Import Division.

If FDA approves the product in the application within 6 months of the shipment's date of entry under the PLAIR, the Agency intends to issue a "Release after Detention" for the drug product. If 6 months elapse without FDA approval, FDA may refuse the application. If FDA refuses admission, the drug product must be exported or destroyed within 90 days.

Upon approval of the relevant drug application, the applicant should immediately send a copy of the approval letter to the ORA Import division at the location at which the product is being detained as well as CDER-OC-PLAIR@fda.hhs.gov. Should there be any deviation between the drug product detained under the granted PLAIR and the provisions in the approved drug application, the applicant should notify FDA of the difference(s).

TAKEAWAYS

Significant Changes from 2013 Draft Guidance

This Final Guidance is the product of a Draft Guidance published by FDA in 2013. While the Final Guidance is largely the same as its draft version, there are two key differences:

1. Timeframes

The maximum timeframes for submissions of PLAIRs were adjusted by FDA to distinguish between those applications that are subject priority (*i.e.*, six months) or standard review. The timeframes for NDAs and CDER-regulated BLAs subject to standard review have remained the same, but in this Final Guidance the Agency requests that all PLAIRs for NDAs and CDER-regulated BLAs subject to priority review be submitted up to 120 days before the user fee goal date.

For ANDAs, FDA originally requested in the Draft Guidance that PLAIRs for abbreviated applications be submitted 60 days "prior to expecting full approval." In this Final Guidance, FDA again separates submission dates based on priority. Now, PLAIRs for ANDAs subject to priority review should be submitted up to 80 days before the user fee goal date. If the ANDA is subject to standard review, FDA requests that, like standard NDAs and CDER-regulated BLAs, the PLAIR be submitted 60 days before the user fee goal date.

2. Contents of a PLAIR

In this Final Guidance, FDA added two items that should be included in a PLAIR that were not present in the 2013 Draft Guidance: (1) a letter from FDA documenting the user fee goal date; and (2) the precise quantities to be imported.

Reviewing Application and Agreements

Since a PLAIR requires the applicant to submit a signed letter stating the location of the facility where products will be warehoused or further processed (if applicable), applicants are encouraged to do the following:

- Confirm the facility where products will be warehoused or further processed (if applicable) are identified in the finished dosage form drug product's pending application (*i.e.*, Module 3);
- Confirm service agreements with vendors/warehouses have clear language permitting the unapproved finished dosage form drug products to be stored at the facility pending approval;
- Confirm service agreements with vendors/warehouses have clear language indicating who will be responsible for ensuring the product remains subject to the terms and conditions of the CBP entry bond that covers the specific shipment;
- Confirm the facility used for warehousing complies with any applicable warehousing/storage current good manufacturing practices as well as applicable federal/state requirement; and
- Confirm service agreements with vendors/warehouses have clear language indicating who will be responsible for exporting or destroying the product if FDA refuses to approve the application or 6 months otherwise elapse without FDA approval and the Agency issues a "Notice of FDA Action-Refusal of Admission."

Relatedly, since a PLAIR requires information concerning the precise quantities to be imported, applicants should leverage any forecast reports generated to determine these amounts.

Time Management is Key

As stated earlier, 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. However, applicants should be aware this is a floor and not the ceiling. As noted earlier, depending on whether the drug application is subject to a standard or priority review, an applicant can submit their PLAIR no more than 60 (standard), 80 (priority ANDA), or 120 (priority

NDAs/CDER-regulated BLAs) days before the user-fee goal date. As a result, applicants are encouraged to incorporate these timeframes in their manufacturing and launch schedules.

Additionally, companies should confirm they have enough stability data and sufficient time remaining prior to product expiration to account for the possibility of up to six months storage.

Final Check

Lastly, as part of the application review process, it is not uncommon for changes to be made to the drug products' labeling which differ from what was provided in the original PLAIR submission. Once an applicant has a final label for the warehoused drug product, the applicant should submit an "amendment" to the PLAIR explaining all the changes made. By informing FDA of these changes and keeping the PLAIR record accurate, the applicant can avoid the detained product from ultimately being refused entry based upon a determination that the product is misbranded under section 502 of the FD&C Act (21 U.S.C. 352) and/or considered an unapproved new drug under section 505 of the FD&C Act merely because the label and supporting PLAIR documentation differ from the approved NDA, ANDA, or BLA.

If you have any questions about the above-described guidance document, please contact the authors listed on this alert.

Trevor LaSalvia, a Project Assistant at Wiley Rein LLP, contributed to this alert.

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1 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.