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Manufacturing site changes for packaging materials and how they impact our pharmaceutical partners

Source by:
West Pharmaceutical Services, Inc.

Executive Summary

In 2021, the Center for Drug Evaluation of the NMPA issued Technical Guidelines for Pharmaceutical Changes Research for Marketed Chemicals (No. 15, 2021), which details NMPA's expectations on management of change with existing registrations for drug preparers. Changes are assessed based on the significance of impact on drug safety, effectiveness, and quality controllability of drugs.The guideline divides changes into three categories: major changes (significant impact), medium changes (medium impact), and minor changes (small impact). Depending on the category, the report type, requirements for verification of the safety, efficacy, and stability of the drug and even the filing agency vary.

West Pharmaceutical Services, Inc. (West) has been successfully filing packaging material filings in China in accordance with "Announcement of Further Improving the Bundling Review, Approval and Supervision of Drug" (No. 56, 2019) since 2019. With over 80 dossiers filed, the number is expected to grow in the next few years. With the increased amount of items filed, tighter controls over life cycle of these dossiers are crucial to meet quality and regulatory compliance.

As the registrant of packaging materials for these packaging material filings, West is required to notify relevant drug preparation manufacturers and the Center of Drug Evaluation (CDE) in China on any changes that impacts the submitted registration information in a timely manner. From there, the drug marketing authorization holders are to review and evaluate the impact to their drug preparations. If impacted, supplementary applications may be required by the drug preparer.

At West, we have an established process to evaluate, process and track all changes within West's manufacturing network. Changes that most commonly impact submitted dossiers include changes in manufacturing facility location, changes in a test method that is not compendial in nature, changes in manufacturing method, or changes to raw materials. Changes in manufacturing sites, including dual manufacturing, manufacturing layouts and processes, are common to help accommodate growing demands in the industry in terms of quality and quantity. In most of these cases, these types of changes do not require a new dossier. Instead, an amendment to the packaging material filing is filed. In the following sections, the different scenarios for manufacturing site changes and subsequent impact for drug preparers are explored.

TYPES OF MANUFACTURING SITE CHANGES

There are three different classifications for amendments to existing Chinese packaging material filings: major, medium, and minor changes. Categorization is based on impact of the final packaging component/system that is filed in China and its possible impact to drug preparers. Table 1 lists the different types of manufacturing changes, associated categorization, and filing strategy for these changes.

Regardless of change type, a majority of these changes will result in an amendment to the existing dossier.

TABLE 1 **Classification of Changes per Manufacturing Site Change**

Change	Change Type	Filing Strategy
Addition of Manufacturing site for pre-release manufacturing steps	Minor	Amendment
Addition of final release manufacturing site	Major	Amendment/ New Dossier*
Change in Manufacturing site for pre-release manufacturing steps	Minor	Amendment
Change in final release manufacturing site	Major	Amendment
Change to existing manufacturing process step	Major	Amendment

*Current Industry practices have limited one release site per dossier. However, West may file as an amendment instead depending on the complexity of the transfer.

WHY IS THIS IMPORTANT?

In 2021, the Center for Drug Evaluation of the NMPA issued Technical Guidelines for Pharmaceutical Changes Research for Marketed Chemicals (No. 15, 2021), which details NMPA's expectations on management of change with existing registrations for drug preparers. Changes are assessed based on the significance of impact on drug safety, effectiveness, and quality controllability of drugs. The guideline divides changes into three categories: major changes (significant impact), medium changes (medium impact), and minor changes (small impact). Depending on the category, the report type, requirements for verification of the safety, efficacy, and stability of the drug and even the filing agency vary as noted in Table 2.

TABLE 2 Classification of Changes and Related Report Type

Classification	Report Type	Filing Agency	
		Domestic Drug	*Import Drug*
Major Change	Supplementary Application	CDE	CDE
Medium Change	File	Provincial	CDE
Minor Change	Annual Report	Provincial	CDE

For changes in packaging materials and containers, the deciding factors on the change classification is mostly centered around change of material or type of packaging materials and containers, change of packaging quantities, or change of supplier, size or shape associated with the route of administration.

Table 3 summarizes the different changes and associated classification of change.

In addition to the below, major changes also include significant changes such as change to new materials or new usages with increase risks and removal of secondary packaging where its original intent was to provide an extra layer of safety.

TABLE 3 Classification of Changes per Drug Type/Route of Administration

Classification	Report Type	Filing Agency	
	Drug Type/ Route of Administration		
Change of:	Minor Change	Medium Change	Major Change
Material or type of packaging materials and containers	APIs and non-sterile solid preparations	Liquid/semi-solid preparations	Inhalation, injection, ophthalmic preparations
Packaging quantities	APIs and single-dose packaging preparations	Multi-dose packaged preparations	NA
Supplier, size or shape	All other preparations	Injection preparations	Inhalation preparations

Bringing it all Together

Changes to packaging materials directly impact the associated marketing authorization holder of the drug. The nature of the change governs how the existing dossier is impacted, and in turn impacts the drug preparer. There is a general rule within No.15 Guidelines which indicates that any changes to the packaging materials that result to a different dossier filing (either not registered yet or an existing dossier that is not active) will be classified as a major change for the drug preparer. However, changes to existing packaging materials that are documented through an amendment can also be considered a major change. West is committed to providing notification of changes to impacted drug preparers to fully assess the impact to their products.

Key Takeaways

Collaboration between packaging material suppliers and pharmaceutical manufacturers is key to minimizing impact when there is a change in packaging material. Transparency of the change and filing methods is important to ensure impacted drug manufacturers make the appropriate assessments for their drug products. The result allows us to continue to serve our customers.

FREQUENTLY ASKED QUESTIONS

Q: What are manufacturing site transfers?

A: Manufacturing site transfers, also known as technology transfers in pharmaceutical manufacturing, is defined as "a logical procedure that controls the transfer of any process together with its documentation and professional expertise between development and manufacture or between manufacture sites."[1] This can include any part of the manufacturing process, from specific manufacturing steps (eg. Compounding, mixing, washing, packaging) to the entire manufacturing of a product to another manufacturing site.

Q: How are China Packaging Filings (aka China DMFs) impacted when manufacturing site transfers occur?

A: Manufacturing processes and manufacturing sites are part of the China Packaging filings. Any changes to the original submitted data requires an amendment to filing. When the change involves allowing multiple manufacturing sites for one product, there is an option to either amend an existing filing or create a new filing. Please see table below for example changes.

CLASSIFICATION OF CHANGES PER MANUFACTURING SITE CHANGE

Change	Filing Strategy
Addition of Manufacturing site for pre-release manufacturing steps	Amendment
Addition of final release manufacturing site	Amendment/ New Dossier*
Change in Manufacturing site for pre-release manufacturing steps	Amendment
Change in final release manufacturing site	Amendment
Change to existing manufacturing process step	Amendment

*Current Industry practices have limited one release site per dossier. However, West may file as an amendment instead depending on the complexity of the transfer.

1 Annex 7. WHO guidelines on the transfer of technology in pharmaceutical manufacturing

Q: Are new letter of authorizations (LoAs) required when there is a manufacturing site transfer?

A: Depends. If the change requires a new dossier, then a new LoA would be required to represent the new site. If an amendment was completed instead, a new LoA would not be required. Our customer change notification process on manufacturing site transfers will provide detailed instructions and actions required by impacted customers.

Q: We just filed a drug application with NMPA with one of West's packaging products. How will a manufacturing transfer impact the drug application?

A: If the manufacturing change results to a new dossier number and the status of this new dossier number is 'I', the drug preparer should evaluate the change and make appropriate application with the China agency per Technical Guidelines for Pharmaceutical Changes Research for Marketed Chemicals (No. 15, 2021) and Technical Guidelines for Pharmaceutical Changes of Marketed Biological Products (No. 31, 2021) once their drug is approved. West will provide a new LoA to customers if required. If an amendment was performed, resulting to no change of the China packaging filing number, the CDE reviewer pulls the most recent amended dossier as part of their review process. No new LOA is required from the drug preparer. The drug company should internally evaluate the impact of changes in the manufacturing site of the packaging material on drugs.

Q. We currently have products in the China marketing utilizing West's packaging materials. How will a manufacturing transfer impact the drug application?

A: There are two possibilities for implementing a manufacturing transfer. The 1st one results to a new dossier number and the status of this new dossier number is 'I'; the second one is that an amendment was performed, no change of the China filing number. Per Technical Guidelines for Pharmaceutical Changes Research for Marketed Chemicals (No. 15, 2021) and Technical Guidelines for Pharmaceutical Changes of Marketed Biological Products (No. 31, 2021), drug preparer are expected to disclose changes based on its classification. Drug companies should evaluate the change and make an appropriate application with China agency. See table below on the classification of Changes and related report type.

		Filing Agency	
Classification	**Report Type**	**Domestic Drug**	**Import Drug**
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Minor Change	Annual Report	Provincial	CDE

West is committed to providing notification of changes to impacted drug preparers to fully assess the impact to their products.

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