Lifecycle Maintenance of Product Registrations in China

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Lifecycle Maintenance of Product Registrations in China

Tigermed Insights

In this blog post, we discuss the essential aspects involved in the lifecycle maintenance of medicinal products with market authorization in China. In addition, we will focus on regulatory compliance, labelling/packaging changes and regulations for promotional materials. Shortly, everything you need to get up to speed with Lifecycle Maintenance of Product Registrations in China.

Regulatory Landscape in China

In 2017, China joined the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). In the following years, the Chinese National Medical Product Administration (NMPA) updated its regulatory framework, among other reasons, to better adhere to international standards and increase the appeal of China's pharmaceutical market.

The Good Manufacturing Practice (GMP) for Drugs and the ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management are essential guidelines for drug lifecycle management. Chinese regulations that have partially included these guidelines are the Drug Administration Law (DAL), Drug Registration Regulation (DRR), the China Pharmacopeia (ChP) and the Provisions for Post-Approval Changes. China has introduced the Market Authorization Holder (MAH) system as part of these regulatory changes. Foreign pharmaceutical companies are required to have a Chinese partner as MAH, which is responsible for drug registration and post-approval studies and lifecycle maintenance.

China has also started to adopt the ICH's Common Technical Document (CTD) format for regulatory submissions. Since the end of 2021, electronic CTD (eCTD) submissions for drug registrations have been possible. The eCTD format is also planned to be used for lifecycle management and variation submissions.

Regulatory Compliance and Post-Approval Variation Management

The ICH Q12 guideline states that the MAH and competent authorities (CAs) have to define established conditions (ECs) in the CTD that are essential elements to ensure product quality. Subsequently, changes to ECs have to be reported to, or approved by, the CA. In China, the CA is the Centre for Drug Evaluation (CDE), part of the NMPA. China is still in the implementation phase for the ICH Q12 guidelines but has already defined three different categories for variations:

Major changes

Major variations include changes to the CMC (chemical, manufacturing and control) aspects of a medicinal product. This can, for instance, be a change to the chemical composition of a drug, an improved production method or a change in quality standards. In addition, changes to a pharmaceutical product's clinical characteristics or the product name are also considered significant changes.

Additionally, a change of the MAH counts as a major variation. This is not uncommon under the Chinese system since foreign companies need a local partner to serve as MAH. In the case of a medicinal product from a foreign MAH, a change in the foreign MAH could be seen as a major variation requiring a supplemental application both abroad and in China. Some changes only concern the local Chinese MAH, such as a change of the name of the MAH or a change in the manufacturing site. In this case, the MAH first has to be approved by the CDE, and subsequently, any potential changes in the CMC have to be reported and approved.

Major changes require a supplemental application that has to be approved by the CDE before implementation. Approval times depend on the type of change, ranging from up to 20 days if only the MAH is changed, 60 days for a single change that requires technical review, 80 days for multiple changes that require review, and 200 days if the changes require inspection or new testing.

Moderate changes

Examples of moderate variations are non-technical changes, such as new manufacturing licences, new local registration agents or moderate changes to packaging. In addition, moderate changes to the technical documentation related to CMC aspects or clinical information, for instance, a further specification of clinical benefits or risks, also fall under this category.

Moderate variations have to be reported to the CDE but do not have to be approved and can, therefore, subsequently be implemented.

Minor changes

> Minor variations include changes to the packaging size or a change to the supplier of excipients, but all specifications remain the same. Minor variations can be implemented immediately and only need to be reported to the CDE in the annual report.
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> It is possible to consult the CDE if the categorization of variations is unclear under certain circumstances. It is also important to assess future changes in regulations and guidelines on variation management, for instance, to ensure that change management tools are suited to incorporate these changes. An example would be when China allows variation management through the eCTD. Furthermore, it is advisable to proactively approach the CDE and NMPA to plan and anticipate future changes.

Labelling and Packaging

Labelling in China must include the medicinal product's name, ingredients and specifications. Clinical information should specify indication(s) of use, primary function(s) and symptoms that are treated, and side effects, precautions and contraindications. You should also specify dosage and administration methods. The MAH and manufacturer have to be mentioned together with the approval number from the NMPA and contact information. Each package should list the product batch number, production date and expiration date. If any special transportation conditions apply, you must specify this on the label and the packaging. Packaging should also show the necessary marks for precautions and warnings, the CE mark, packing quantity and storage and transport conditions. If variations in the CMC, technical or clinical information or other aspects are approved and/or implemented, the drug label and packaging must be updated accordingly.

Promotional Materials

Promotional materials must be accurate and based on scientific evidence and should not be misleading or based on unproven claims. Using the names of medical institutes, scientists, patients or other experts to promote a product commercially is not allowed. Prescription drugs can only be advertised in NMPA-approved medical and pharmaceutical journals, whereas over-the-counter drugs can be advertised to the public directly. To promote medicinal products, you have to apply for approval for each advertisement with the NMPA. An advertisement approval number is valid for one year. These regulations apply to both paper-based promotional materials and online advertisements on websites or social media.

Concluding Remarks

The implementation of ICH Q12 guidelines and post-approval change management, in general, are still under development in China. Familiarity with Chinese regulations, guidelines, and voluntary industry standards such as the Pharmaceutical Industry Compliance Management Practices (PICMP) is essential for successful navigation in the Chinese regulatory landscape. Since these regulations and the Provisions for Post-Approval Changes are not exhaustive and sometimes unclear, it is helpful to have an experienced local partner. A local partner can provide knowledge about post-approval change management, labelling and packaging regulations, and promoting medicinal products in China and can offer an existing working relationship with the NMPA, CDE, and other local stakeholders.

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