Implications of China’s New Excipient Dossier “Bundling Review” Requirements Explored at IPEC-Americas ExcipientFest Workshop

Global excipient and pharmaceutical manufacturers are weighing the complexities and consequences of the new “bundling review” requirement put in place by the China Food and Drug Administration (CFDA) in August 2016, which calls for excipient dossiers to be received, reviewed and approved as part of new drug applications.

Prior to the new requirements, an excipient supplier could prepare and submit an import drug license (IDL) for review and approval by a local province, FDA or CFDA. Under the new “bundling review,” the information on the excipient is submitted along with a specific drug application, with the excipient then getting approval for use in similar drug products (having the same route of delivery, the same or lower level of use, and the same supplier/grade of excipient) once the new drug product is approved.

The challenges created by the changing requirements in China were explored at an IPEC-Americas workshop on global excipient regulatory strategies that preceded the ExcipientFest conference held in Providence, Rhode Island, in late April. The workshop focused on the evolving regulatory requirements in Korea and Brazil, along with those in China.

Piggybacking off of a presentation at an IPEC Europe conference in February 2017 given by Colorcon China Regulatory Affairs Manager Colin Li, who is Chair of IPEC China, Colorcon Global Regulatory Affairs Director Dave Schoneker took the IPEC-Americas workshop attendees through the changes to the excipient regulations in China, the excipient dossier requirements for the bundling review published by CFDA in late November, 2016, and the challenges that the new regulatory approach creates for global companies. Schoneker is Vice-Chair of IPEC-Americas Science and Regulatory Policy.

He explained how the previous process allowed the excipient supplier to apply for an IDL, independent of a drug application, and for a drug manufacturer to refer to the excipient license in their application.

However, the new bundling process now requires the excipient supplier to partner directly with the drug applicant in submitting a dossier to the CFDA that contains all relevant information to support a drug application. Based on this new process, the excipient supplier can no longer get an independent review/approval.
This new approval process will be especially challenging for distributors, Schoneker noted, who will have to work with their excipient manufacturers to a much greater degree and, at least for the first use of an excipient for a given route of delivery, will need to facilitate direct dialog between the excipient manufacturer and the drug applicant.

Once an excipient gets approved in a new drug in China using the bundling process, the excipient will be assigned a reference number, which can then be used in support of other new drug applications using the same excipient (both manufacturer and grade), the same or lower use level, and the same route of delivery.

In addition, change control will be key, Schoneker stressed. Any change, including a change of the excipient recipe, process or specification(s), that could have an impact on drug product quality will require the excipient manufacturer to evaluate the change, notify the drug manufacturer(s), and submit information to support the change directly to the CFDA. He noted that the details of the change control process and requirements have not yet been published, complicating the transition process.

**Transition Period and Exemptions**

To help facilitate the transition, CFDA has agreed that both an excipient license and approval number will be waived for excipients already used in drugs that were approved in China prior to August 2016. However, excipients used in approved drugs imported into China may be required to provide evidence that the excipients are a pharmaceutical grade, and when applicable, that they meet the ChP. In addition, the CFDA has extended the expiry date of excipients with pending or expired IDLs to December 31, 2017.
For new drugs currently going through the approval process in China, it is now mandatory for the excipient suppliers to partner with a drug company to ensure it understands the requirements and documentation necessary for the CFDA review. Although it is critical for the excipient supplier to bundle and submit the necessary information along with the drug application, depending on the confidentiality of the information, it can either be submitted to the CFDA through the drug application holder or directly by the excipient manufacturer to the CFDA at the time the drug application is filed.

**Excipient Dossier Requirements**

As published in November 2016, the excipient dossier requirements under this new China bundling process are very detailed and extensive, especially for manufacturing information where detailed information on such things as the manufacturing process, process controls and process equipment used (including serial numbers and equipment manufacturer) is required. In addition, the excipient dossier now needs to include full copies of validation and process development reports.

“There is a lot of intellectual property at stake…beyond the science point, in a lot of companies’ perspective,” Schoneker pointed out.

He stressed that the requirement for bundling the excipient dossier into the new drug application makes it imperative for excipient considerations to be included in the drug development process for new products in order to avoid any possible approval delays. In addition, any excipient change that could have an impact on the quality of an approved drug product will need to be evaluated and justified to both the drug product manufacturer and CFDA.

Other possible excipient concerns in China include the growing importance of the Chinese Pharmacopoeia (ChP) in the regulation of excipients, and the possibility that imported drugs – currently exempted from these excipient bundling registration rules - will in time fall under the same requirements as domestically-produced medicines. Excipients manufactured outside of China could be included in inspection programs, based on risk.

[A full review of the insights offered at the IPEC-Americas workshop on the changing excipient regulatory landscape in China, Brazil and Korea will be provided in IPQ’s upcoming Monthly Update. By special arrangement with IPEC, excipient suppliers who are members can receive a company-wide license for the normal price of the subscription for an individual user. The license allows everyone in a company to access all of IPQ’s coverage of the key drug/biotech CMC and GMP issues globally and the full searchable archives. Contact Wayne Rhodes (rhodes@IPQPubs.com, (202) 841-9720) for more information. IPQ will be providing in-depth coverage of a key excipient regulatory issue in each of its Monthly Updates, with an excerpt included in IPEC’s Insider.]

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