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CHINA RELEASES PROPOSED GUIDANCE ON THE DEVELOPMENT OF SIMILAR BIOTHERAPEUTIC PRODUCTS

On October 29, 2014, the Center for Drug Evaluation (CDE) of the China Food and Drug Administration (CFDA) released proposed Guidance on the Research and Development and Technical Evaluation of Similar Biotherapeutic Products (Draft SBP Guidance or the Draft Guidance). The Draft SBP Guidance is a long-awaited next step in China towards the adoption of a more concrete and well-defined regulatory pathway for SBPs (also known as "biosimilars"). CFDA has solicited public comments on the Draft Guidance. Comments are due on November 29, 2014.

Currently, China permits applications for biologics that follow a pre-existing "biological product standard" in China. This allows follow-on products that are classified as "Categories 13-15" to come to market under reduced data requirements, such as requiring only Phase III clinical trial data. This is controversial because the pre-existing standard is not necessarily representative of an innovative product supported by a full clinical data package, and the CFDA has significant discretion to reduce or waive certain clinical data and other application requirements. Current Chinese drug laws and regulations do not contain definitions (e.g., of an innovative biologic or "reference product") to permit the kind of intensive comparison that occurs between biosimilars and reference products under the biosimilar regulatory pathways in many other jurisdictions (such as the United States, the European Union, and Japan, and as contemplated under World Health Organization (WHO) guidelines). The Draft SBP Guidance is a step forward in this direction.

The Draft SBP Guidance states that it is intended to guide the research and development of biosimilars and promote the development of the biopharmaceutical industry in China. It also notes that biologics have been proven to have significant clinical advantages in the treatment of life-threatening diseases. Even so, China has approved a very small number of biologics per year compared with small molecule drugs, and the waiting time for the necessary approval to begin research and development is nearly double that for small molecule drugs in some cases. It can take up to two years just to obtain approval to conduct the necessary clinical trial to bring a biologic to market.

The Draft SBP Guidance states that applicants "shall" follow it in the research and development of SBPs, but the requirements of Chinese drug law will continue to apply. This indicates that CDE, which is responsible for the technical evaluation of applications to conduct clinical trials and register biologics, will expect compliance with the Draft SPB Guidance to the extent applicable, but the Draft Guidance will not supersede requirements in the Drug Administration Law and the Drug Registration Regulations, which remain the primary pieces of legislation governing the drug and biologic research and development and approval processes. It is unlikely, therefore, that the Draft SBP Guidance will change many of the existing impediments to the development and approval of biologics in China.

Under the Draft SBP Guidance, an SPB must be similar to a reference product in terms of quality, safety and efficacy. Reference products are defined as "innovative" products used as the comparator during the development of an SPB that are authorized by CFDA for marketing in China.

The Draft Guidance specifies that "in principle, an SBP should not be used as a reference product." The Draft Guidance also notes that if the reference product cannot be obtained by commercial means in China, "other appropriate means can be considered." Notably, the Chinese term used for "innovative" is not further defined under the Draft SBP Guidance or defined under current Chinese drug law and regulation. Therefore, its relationship to other concepts, such as that of a "new drug" is unclear.

Pursuant to China's Drug Registration Regulations, all biologics (whether truly new or authorized under a pre-existing standard) follow a "new drug" pathway to market. The relationship between these existing provisions and the SBP approval requirements described in the Draft Guidance is not clear.

The Draft SBP Guidance sets forth general principles for research and development and evaluation of recombinant therapeutic proteins that have well characterized and defined structures. These principles are generally consistent with the WHO guidelines. They include the principles of comparability, meaning that SPBs should be evaluated at each development stage against reference products; the principle of stepwise development, meaning that applicants generally should conduct analytical testing, then nonclinical testing, then clinical testing to demonstrate similarity; and the principle that in some cases testing requirements may be reduced based on the results of earlier stage testing.

The Draft Guidance describes considerations relevant to analytical, nonclinical, and clinical testing. If comparative quality studies clearly show only small differences between the SBP and the reference product, nonclinical data may be limited to comparative pharmacodynamics, pharmacokinetics, and immunogenicity studies. The Draft Guidance calls for a graduated approach to clinical studies, beginning with pharmacokinetic and pharmacodynamics studies. When these comparative studies show differences or uncertainty regarding similarity, then comparative clinical safety and efficacy trials must be conducted. On the other hand, when these comparative studies show no or little differences or uncertainty regarding similarity, the wording of the Draft Guidance may be interpreted as not requiring further comparative clinical safety and efficacy trials.

The Draft SBP Guidance also includes very brief and general sections on package inserts and pharmacovigilance. The package insert for the SBP and reference product should "in principal" be the same, including the indications, dosage form and strength, and safety information, except where the SBP is approved for fewer indications than the originator product. The pharmacovigilance section requires that applicants submit a postmarket risk management plan. This section is consistent with China's growing emphasis on developing new and more in depth measures for postmarketing surveillance.

Overall, the Draft SPB Guidance represents an important milestone in the development of a biosimilar pathway in China. Many of the points in the Draft Guidance will require elaboration and clarification, particularly at the scientific level. The greatest challenge, however, will likely be the integration of the Draft Guidance's framework into the existing regulations for biologic approval in a workable manner. Companies manufacturing or importing biologics in China should continue to monitor these development and consider submitting comments.

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