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# Biosimilars are Regulated Differently in China

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The Center for Drug Evaluation (CDE), the technical review body under the China Food and Drug Administration (CFDA), released the Technical Guideline for the Research, Development and Evaluation of Biosimilars (Tentative) (Guideline) on February 28, 2015. This long-awaited Guideline outlines the regulatory framework for biosimilars, aiming to address clinical needs for biologics in China by improving the accessibility and affordability of innovative products. Both local and foreign biologics manufacturers have all been closely following the Guideline and its implementation, as it presents an alternative option for launching biologics in China.

The newly released Guideline sets forth the definition of biosimilars and their reference products, the basic principles for the technical review, the criteria for comparability, and the conditions under which extrapolations of indications would be permissible. Pursuant to the Guideline, a biosimilar drug should in principle have the same amino acid sequence as the reference product. Similar to the regulatory authorities in the U.S. and European Union, the CDE expects a detailed structural and functional characterization of the biosimilar drug when comparing the same to the reference product. The CDE also takes a similar step-wise approach to examine comparability through comparative pharmacology data, non-clinical studies, and clinical studies.

Despite sharing the same principles for technical reviews, the Guideline presents notable differences from the U.S. and European regimes. First, biosimilars are not assigned to a separate abbreviated approval pathway in China; they are subject to the same approval pathway as innovative biologics. Secondly, the CDE does not accept an innovative biologic approved by foreign regulatory authorities as a reference product. The reference product can be pending for

CFDA approval during early stages of the biosimilar development process, but must be approved by the CFDA when comparative clinical studies are conducted. Last but not least, first-to-market biosimilars are not entitled to any regulatory exclusivity in China. These differences are elaborated in detail below.

| Comparative Overview | | | |
|---|---|---|---|
| | China | Europe | U.S. |
| **Regulatory System** | A single technical guideline released by CFDA | An overarching biosimilars regulation, and a series of product-class-specific guidelines | The Biologics Price Competition and Innovation Act and seven supporting guidelines |
| **Approval Pathway** | Subject to the new drug approval pathway with customized technical review criteria | Subject to an abbreviated approval pathway and reviewed by EMA centrally | Subject to an abbreviated licensure pathway |
| **Choice of Reference Product** | Approved in China or elsewhere during analytical and non-clinical studies; China-approved if used in clinical studies | EMA licensed, or licensed in a country with similar scientific & regulatory standards as EMA's if able to establish an acceptable bridge | FDA licensed or non-U.S.-licensed if able to establish an acceptable bridge to a U.S. licensed reference product |
| **Requirements for Safety and Efficacy Studies** | Potential simplification allowed if limited differences in previous studies and biosimilarity can be inferred from clinical PK/PD; confirmatory trials generally not waivable | Risk-based approach on a case-by-case basis; possible to approve biosimilars based on PK comparative study and supportive PD data, without comparative efficacy studies | Necessary if residual uncertainties of biosimilarity are inferred from analytical and animal studies, but omission of certain comparisons on clinical safety and effectiveness is possible upon provision of scientific justifications |
| **Exclusivity Period** | The "new drug monitoring period" only applies to locally manufactured innovative biologics | A biosimilar may not be approved until 10 years after the approval of the reference drug | - The first biosimilar approved as an interchangeable is entitled to a period of exclusivity<br>- A biosimilar may not be approved until 12 years after the approval of the reference product |
| **Interchangeability** | No guidance yet | EMA leaves decision on substitution to national competent authorities of EU member states | Possibly available for products with the same clinical results as reference product's in any given patient and having no greater risk in safety or diminished efficacy to switch to the biosimilar |
| Source: Ropes & Gray, PharmaDJ | | | |

## Overall Regulatory Approach

The Guideline serves as a stand-alone technical guidance; it is not derived from any overarching law (e.g. the Drug Administration Law) or regulations (i.e. the Drug Registration Rules). As technical guidance, the Guideline cannot address several fundamental issues for the administration of biosimilars in the absence of a clear legislative authorization, e.g. interchangeability with the reference product, the naming rules and labelling requirements for biosimilars. These issues will need to be addressed by law or regulations. Furthermore, the CDE has not substantiated the Guideline by detailed guidance specific to the stages of biosimilar development or product categories.

By comparison, the U.S. FDA and the EMA both regulate biosimilars with a combination of law, regulations and technical guidance. The technical guidance documents address for each of the major product categories and each stage of the biosimilar development process. The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) passed under the Patient Protection and Affordable Care Act of 2010, creates an abbreviated licensure pathway for biosimilars in the U.S. From 2012 to 2015, the U.S. FDA published seven guidance, both final and draft, to implement the law, covering the scientific and quality considerations in demonstrating comparability as well as several procedural issues such as exclusivity.

## Approval Pathway

Other than creating a set of technical review principles which differ from those applicable to innovative biologics, the Guideline does not create any separate pathway for biosimilars due to the absence of legislative authorization. Biosimilars are essentially subject to the same approval pathway as innovative biologics, with a different set of data requirements. Companies must mark in their IND and NDA applications that submissions are intended to be reviewed as biosimilars.

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In EU and the U.S., biosimilars are entitled to an abbreviated approval pathway. For example, in the U.S., the BPCI Act creates an abbreviated licensure pathway for biosimilars under Section 351(k) of the Public Health Service Act. A biosimilar may rely on, among other things, "publicly available information regarding the U.S. FDA's previous findings and determination that the reference product is safe, pure and potent and may not be required to provide full product-specific non-clinical and clinical data". The actual approval timeline under the biosimilars pathway is also notably faster than novel biologics. **Novartis AG** filed 351(k) application for *Zarxio* in July 2014, and based on review of evidence that demonstrated Zarxio to be comparable to **Amgen**'s *Neupogen*, in March 2015 the U.S. FDA approved Zarxio as the first biosimilar for use in the U.S. in nine months after receiving Novartis' application.

## Choice of Reference Product

In China, a reference product used in analytical and pre-clinical studies can be approved in China or elsewhere. However, the same reference product must be approved in China at the time when comparative clinical studies are initiated. The reference product should be usually, but not always, the originator's product. Approved biosimilars themselves cannot act as reference products.

Under the U.S. and EU regimes, as long as an acceptable bridge could be established between the reference product and the EU-approved or U.S.-approved products, products approved outside the EU or the U.S. could also be the reference products. Furthermore in Europe, a foreign licensed reference product must be approved in a country or region with similar scientific and regulatory standards as the EMA's.

## Requirements for Safety and Efficacy Studies

The CDE Guideline allows reduced pre-clinical and clinical data requirements under the condition that no significant differences are identified in pharmacology or analytical comparisons. This can be demonstrated by establishing comparability in production processes, physical and chemical properties, potency, purity, etc. However, the Guideline is not clear on whether large-scale confirmatory clinical studies can be waived even if comparative PK/PD studies and immunogenicity studies are performed on patients and have demonstrated high comparability.

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The EMA's guidelines, on the contrary, offer a risk-based approach, under which the scope of studies will depend on product complexity, the inherent ability to be characterized by quality parameters, and the mode of actions across indications. The EMA's updated overarching guideline for biosimilars, effective as of 30 April 2015, specifically provides for the possibility of a biosimilar approval based on pharmacokinetic

comparative studies and supportive pharmacodynamic data, without comparative efficacy studies.

## Regulatory Exclusivity

Similar to small molecule generics in China, there is no exclusivity protection for the first-to-market biosimilars. The first approved biosimilar will not have additional competitive advantages in market access.

In the U.S., a one-year exclusivity period is granted to the first biosimilars determined to be interchangeable with the reference product for any condition of use. During this period, no other biosimilars may be deemed interchangeable with that reference product.

Separately, China has a relative shorter exclusivity period for first-approved pioneer drugs. There is only a "new drug monitoring period" of up to five years to fence off follow-on applications, and the protection only applies to locally-manufactured new drugs. Market entry of biosimilars in China is mainly restricted by patent exclusivity. In the U.S. and Europe, biosimilars cannot be approved until 10 or more years after the approval of the reference product. This regulatory exclusivity can balance the interests between innovative biologics manufacturers and biosimilar manufacturers.

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## Interchangeability

"Interchangeability" generally refers to the fact that a biosimilar can produce the same clinical results as the reference product in any given patients and has no greater risk in safety or diminished efficacy to switch between the biosimilar and its reference product.

The CDE Guideline does not mention the concept of interchangeability, while the EMA leaves it to the discretion of national competent authorities of each EU

member state. In the U.S., if a biosimilar is deemed interchangeable, pharmacists may substitute the reference product by the biosimilar, without specific instructions from the healthcare providers who prescribe the reference product. If the biosimilar is not interchangeable, the healthcare providers will refer to the specific name of the biosimilar in the prescription note in order for pharmacists to dispense the biosimilar.

The publication of the Chinese Guideline represents a significant progress to promote the development of biosimilars. Patients are expected to have access to more affordable biologics in China. At this early formative stage of biosimilar regulations in China, the Guideline presents a good starting point for biopharmaceutical companies to weigh advantages against disadvantages when choosing between China's new biosimilar pathway and the pathways in other foreign jurisdictions.

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## About Authors:

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