

as LMWH have been excluded from the guideline. Another class of product excluded is synthetic peptides, since the desired synthetic peptides can be easily defined by structural analyses and can be defined as generic drugs. Similar to the requirements of the EU, the original biologic should be already approved in Japan. However, there are some differences in the requirements of stability test and toxicology studies for impurities in biosimilars between the EU and Japan. A comparison of the stability of a biosimilar with the reference innovator products as a strategy for development of biosimilars is not always necessary in Japan. In addition, it is not required to evaluate the safety of impurities in the biosimilar product through nonclinical studies without comparison to the original product. According to this guideline, follow-on biologics such as Somatropin and Epoetin alfa BS have been approved in Japan.

8.2.4.2 Korean Food and Drug Administration

In Korea, the Pharmaceutical Affairs Act is the high-level regulation to license all medicines, including biological products. The Korean Food and Drug Administration (KFDA) notifications serve as a lower-level regulation. Biological products and biosimilars are subject to the *Notification of the Regulation on Review and Authorization of Biological Products*. The KFDA actively participates to promote a public dialogue on biosimilar issues. In 2008 and 2009, the KFDA held two public meetings and cosponsored a workshop to gather input on scientific and technical issues. The regulatory framework of biosimilar products in Korea is a three-tiered system: (1) Pharmaceutical Affairs Act; (2) Notification of the Regulation on Review and Authorization of Biological Products; and (3) *Guideline on Evaluation of Biosimilar Products* (KFDA, 2011; Suh and Park, 2011).

As the Korean guideline for biosimilar products was developed along with that of the WHO (WHO, 2009), most of the requirements are similar except for that of the clinical evaluation to demonstrate similarity. The KFDA requires that equivalent rather than noninferior efficacy should be shown in order to open the possibility of extrapolation of efficacy data to other indications of the reference product. Equivalence margins need to be predefined and justified, and should be established within the range that is judged not to be clinically different from reference products in clinical regards.

8.2.4.3 China Food and Drug Administration

The Center for Drug Evaluation (CDE) of the China Food and Drug Administration (CFDA) published a draft guidance for comments on October 29, 2014 (CFDA, 2014). CFDA finalized the draft guidance and published a current trial version on February 28, 2015 (CFDA, 2015). In this version, one significant change is to relax the regulation for the selection of reference product for comparison. In the version for comments, CFDA requires the reference product to be the originator product authorized by CFDA. In the current trial version, CFDA has removed this restriction. In other words, EU-approved and/or US-licensed reference products can be used as the reference products. In addition, for PK studies, the traditional 80%–125% equivalence range is not mandatory. In the current trial version, CFDA indicates that an alternative equivalence range (e.g., scaled average bioequivalence for highly variable drugs) can be used if scientifically justifiable.