TABLE 6.1
Updates of Product-Specific EMA Biosimilar Guidelines

Product-Specific EMA Biosimilar Guidelines	Date of First Publication	Date of Revision
Recombinant human insulin	June 2006	September 2015, includes stepwise approach
Somatropin	June 2006	Revision is needed to include the stepwise approach
Recombinant granulocyte-colony stimulating factor	June 2006	Ongoing Concept May 2015, includes stepwise approach
Recombinant erythropoietins	July 2006	Revised in September 2010, but further revision is needed to include the stepwise approach
Recombinant interferon alpha	April 2009	Revision is planned to include the stepwise approach
Low molecular weight heparins	October 2009	Ongoing Draft January 2013, includes stepwise approach
Monoclonal antibodies	December 2012, includes stepwise approach	
Interferon beta	September 2013, includes stepwise approach	
Recombinant follicle stimulating hormone	September 2013, includes stepwise approach	

In the initial European overarching and product-specific guidance documents on biosimilars published between June 2006 and October 2009 [including recombinant human insulin, somatropin, recombinant granulocyte-colony stimulating factor, recombinant erythropoietins, recombinant interferon alpha, low-molecular-weight heparins (Table 6.1)], a nonclinical package for a biosimilar development was expected to consist of comparative *in vitro* bioassays and *in vivo* studies (when a relevant animal model is available), including a pharmacodynamic study and/or at least a repeated dose toxicology study, and in many cases local tolerance studies. However, as more knowledge and experience in the development of biosimilars were gained, and more specifically, when the field was widened to biosimilar monoclonal antibodies (mAbs), it became clear that this standard approach was not appropriate.

6.4 THE THREE Rs PRINCIPLE

Since the introduction of the regulatory need to study medicinal products in animals, there has been a continuous debate on the scientific basis of the predictability of animal studies—in other words its translational value for the pharmacological and toxicological effects of medicinal products in humans and how and when animal studies should be conducted (van Meer et al., 2015b).