colony-stimulating factor, erythropoietin, follitropin, TNF-inhibitor, and insulin for use in the EU; some products were withdrawn (Declerck et al., 2016). The EMA has issued many guidelines for biosimilars, including several product class–specific guidelines. An updated general guideline on biosimilars was issued in 2014 (EMA, 2014).

Only the EMA can grant marketing authorization for biosimilars in the European Union. More precisely, the European Commission issues decisions concerning the authorization of these medicinal products on the basis of the scientific opinions from the EMA. The resulting marketing authorization is valid in all EU member states.

For granting approval for a biosimilar product, the EMA requires clinical trials, including comparability studies to the originator product, to demonstrate safety and efficacy. Additionally, the prospective market authorization holder also must demonstrate lack or at least comparable immunogenicity in long-term clinical trials. Guidelines have been established to provide further details on specific needs to demonstrate biosimilarity for nine primary product classes.

Interchangeability issues are not discussed by the EMA but are a matter for the national competent authorities (Weise et al., 2012). Long-term clinical investigations and systematic monitoring of the efficacy and tolerability of biosimilars in all indications are still needed (Declerck et al., 2010), and even then establishing the interchangeability of biosimilar and reference products will be difficult. One should also take into account that some biosimilars may not carry the same indications as those for which the reference drug is approved. Furthermore, individual regions do exercise their own discretion in regard to the approval of biosimilars for all the indications assigned to the originator drug. For example, in January 2014, Health Canada approved two brands of the monoclonal antibody infliximab as "subsequent-entry biologics" for some (but not all) approved indications of the existing brand (Declerck et al., 2015; Scott et al., 2015). For a recently approved biosimilar of etanercept, the use in children is excluded because low-dose formulations are not available (EMA, 2015). It is beyond any doubt that such situations complicate the real-life application of any "interchangeability" consideration.

The EMA has made it clear that a biosimilar is not the same as a generic drug and has handed the interchangeability issue over to individual countries. As an EMA document states (EMA, 2009): "The EMA evaluates biosimilar medicines for authorization purposes. The Agency's evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. For questions related to switching from one biological medicine to another, patients should speak to their doctor or pharmacist."

In the absence of central European directives, the 28 member states follow diverse directions. In several countries, either legislation has been passed or regulations prohibit automatic substitution by pharmacists (Thimmaraju et al., 2015). Given that most currently approved biosimilars are applicable only in hospital settings, the impact of such a strict prohibition is moderate. At the other extreme, some countries (e.g., Poland and Bulgaria) have no relevant law or guidelines and permit automatic substitution. Substitution is conditional in several other countries (Thimmaraju et al., 2015) and is often restricted to treatment-naïve patients.

Equally important is the reimbursement policy (Declerck and Simoens, 2012), where there are many national variations. One of the options is that new patients