2.3.2.14 Impurity versus attributes

When a new pharmaceutical product is developed, any component other than the key element is suspected of being an impurity, which by definition is undesirable. ICH guidelines properly treat this subject, how the impurities are to be identified, what the critical levels are, and how to justify certain levels of these impurities. In the case of a biopharmaceutical product, the number of components is almost always more than what are found in pharmaceuticals; some of these are product-related impurities, some are process-related impurities, and some are structure-related components. For example, the various glycoforms are the variants, deamidation species, impurities, and the level of host-cell proteins and process-related components. When developing biosimilar products, the identification is further narrowed by the fingerprint provided by the originator product; the sponsor needs to replicate all attributes, components, and even in some cases impurities. Examples in point are the lysine variants found in adalimumab; scientific literature states that these are not clinically meaningful, and the FDA may agree with this. However, recent studies by the originator have begun to show that these components are significant, apparently to keep the competition out since there is an IP coverage on how to manage the lysine variants. The biosimilar developer is faced with the dilemma of going into the market with a product with a different profile, which may be acceptable to the FDA, but it will create a problem in marketing the product, as the originator will obviously make a big deal out of it.

2.3 Biosimilars in use

Biosimilar products have been in wide use in the developing countries, well before the regulated markets of the European Union (EU), Japan, or the United States came to recognize them. The early adoption of biosimilars in developing country markets was driven by the affordability issue, and in several global regions, these products were marketed despite IP protections in place. As a result, there is a long history of the use of biosimilars globally; whereas, in many of these countries, there may not be a formal system of properly reporting adverse events. The consensus is that there have not been any catastrophic results, the only major incidence being reported for erythropoietin in Europe. However, given that the adverse events to biological products may appear even years after their use in the form of compromised autoimmune disorders and the fact that these adverse events are tough to associate with the utilization of a particular product, the regulatory agencies in the developed world have taken a very conservative approach to approving biosimilar products. Many countries that had jumped the gun in approving these products are now adopting a new look at their approval process as the awareness about biosimilar products increases.

Europe has seen the most advanced penetration to date of true biosimilars, authorizing the first product in 2006. While developing nations