reference product by a pharmacist without the intervention of the healthcare provider who prescribed the reference product.

The FDA requires licensed biosimilar and interchangeable biological products to meet the FDA's rigorous standards of safety and efficacy. That means patients and healthcare professionals will be able to rely on the safety and the effectiveness of the biosimilar or interchangeable product, just as they would for the reference product.

2.2.4 The FDA stance

The FDA has taken several bold steps in approving complex products. A case in point is the approval of the generic product enoxaparin; when challenged why no clinical studies were mandated for approval while European Medicines Agency (EMA) requires them, the FDA responded:

> "Although the EMA Guideline requires clinical studies to demonstrate comparable effectiveness to a similar LMWH [low–molecular weight heparin], the FDA notes that its approach (i.e., the five criteria) is more sensitive to differences between two enoxaparin products than the clinical studies recommended in the EMA guideline" (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220037.htm).

While EMA has long established that a clinical trial is needed to establish biosimilarity, the most recent revision of EMA guidance now includes the following statement:

> "In specific circumstances, a confirmatory clinical trial may not be necessary. This requires that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product. In addition, it requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concern" (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf).

2.2.5 351(k) Terminology

2.2.5.1 Innovator versus originator

In the small chemical fields, when a new molecule is synthesized, isolated, or identified, the credit goes to the innovator—as many of them may end up getting a patent for the discovery. However, when it comes to biologics, there can be a differentiation. For example, filgrastim is an endogenous compound and a company discovering a gene to manufacture this product using recombinant technology will qualify as the originator, but not as an innovator. However, when filgrastim is pegylated (the form that does not exist in the body), this qualifies the sponsor as an innovator.