used in the context of regulatory approval. According to comments from FDA officials, the US Congress authorized the FDA to grant approval to drugs that are biosimilars, where the source of motivation was to improve access of the public to drugs that are biologicals (161).

A "biosimilar" is a biological that is similar to, or nearly identical to, an existing FDA-approved reference biological. A corresponding term exists for small-molecule drugs, where this term is "generic drug." Generic drugs are usually small molecules that are absolutely identical to an existing, reference drug. It is difficult for two different manufacturers to produce biologicals that are identical to each other, because of variability in post-translational modification, such as, glycosylation, phosphorylation (162), and carboxylation (163), because of differences in degradation, aggregation, or deamination (164), in view of differences in conformational changes (165), as well as in immunogenicity. Processes for synthesizing biologicals, such as the production of recombinant antibodies by cell culture, and conditions of storage (time; temperature) have a much greater influence on biologicals than on small molecules.

The FDA defines a biosimilar as, "the biological product is highly similar to the reference product notwithstanding minor differences in clinically meaningful differences between the biological product in terms of safety, purity, and potency of the product," adding that, for a biosimilar, "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product" (166).

Where a Sponsor wishes to gain FDA-approval of a biosimilar, the FDA recommends conducting side-by-side tests of the biosimilar and the reference compound. In this recommendation, the FDA stated that, "analytical studies and at least one clinical pharmacokinetic ... study ... must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product" (167).

VII. ORIGIN OF DRUGS THAT ARE ORPHAN DRUGS

a. Rare Diseases

The Orphan Drug Act classifies a rare disease as one that afflicts under 200,000 people in the United States. About 5000–8000 rare conditions exist in the United States and Europe. In the United States, about 25 million people (8%) are afflicted with rare diseases (168). Rare diseases include Fabry's

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