(2) internal review team meeting, (3) internal CDER BRC (CBER BRC) meeting, (4) internal post-BRC meeting, and (5) applicant meeting with CDER (CBER).

Another important issue that arose from the BPCI Act is the interchangeability of biosimilars. Once approved, in many states standard generic drugs can be automatically substituted for the reference product without the intervention of the health care provider. However, the automatic interchangeability cannot be applied to all biosimilars. To meet the higher standard of interchangeability, a sponsor must demonstrate that the biosimilar products can be expected to produce the same clinical result as the reference product in any given patient.

On February 9, 2012, the FDA announced the publication of three draft guidance documents to help industry develop follow-on biologic products, including (1) *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, (2) *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product*, and (3) *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, which were subsequently finalized in 2015 (FDA, 2015a,b,c). Subsequently, the FDA hosted another public hearing on the discussion of these draft guidances at the FDA on May 11, 2012. Similar to the requirements of the WHO and EMA, the FDA considers a number of factors important when assessing applications for biosimilars, including the robustness of the manufacturing process, the demonstrated structural similarity, the extent to which mechanism of action was understood, the existence of valid, mechanistically related pharmacodynamic assays, comparative pharmacokinetics and immunogenicity, and the amount of clinical data and experience available with the original products. The guidances were finalized in early 2015. Even though they do not provide clear standards for assessing biosimilar products, they are the first step toward removing the uncertainties surrounding the biosimilar approval pathway in the United States.

Recently, following the Advisory Committee's recommendation for approval of a proposed biosimilar (by Novartis) to Amgen's Neupogen (filgrastim) on January 7, 2015, the FDA approved the proposed biosimilar on March 26, 2015. Neupogen was originally approved by the FDA in 1991, and its patent expired in December 2013. Neupogen was intended to decrease the incidence of infection, as manifested by febrile neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia. It should be noted that the approved biosimilar of filgrastim is different from Teva's Neutroval approved by the FDA in August 2012. The approval of Teva's Neutroval was based on a full biologic license application rather than under the FDA's new biosimilar approval pathway which allows Teva to compete directly with Amgen's filgrastim in the United States.

8.2.3.2 Canada (Health Canada)

Health Canada, the federal regulatory authority that evaluates the safety, efficacy, and quality of drugs available in Canada also recognizes that with the expiration of patents for biological drugs, manufacturers may be interested in pursuing subsequent entry versions of these biologic drugs which are called subsequent entry