demonstrate safety, purity, and potency in an appropriate condition of use, the applicant may seek licensure of the proposed product for one or more additional terms of use for which the reference product is licensed. However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.

Such scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use:

- The MOA in each condition of use for which licensure is sought; this may include the following:
  - The target/receptors for each relevant activity/function of the product
  - The binding, the dose/concentration–response, and the pattern of molecular signaling upon engagement of target/receptors
  - The relationships between product structure and target/receptor interactions
  - The location and expression of the target/receptors
- The PK and biodistribution of the product in different patient populations (relevant PD measures may also provide important information on the MOA)
- The immunogenicity of the product in different patient populations
- Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to off-target activities)
- Any other factor that may affect the safety or the efficacy of the product in each condition of use and patient population for which licensure is sought

The sponsor of a proposed product may obtain licensure only for a condition of use that has been previously licensed as the reference product. If a reference product has a condition of use that was licensed under Section 506(c) of the FDCA and 21 CFR part 601, subpart E (accelerated approval), and the reference product's clinical benefit in this condition of use has not yet been verified in postmarketing studies, the proposed product sponsor should consider studying another condition of use for which the reference product is licensed to avoid potential complications in the event that postmarketing studies fail to verify the clinical benefit of the reference product for the condition of use.

3.5 Postmarketing safety monitoring considerations

Robust postmarketing safety monitoring is an important component in ensuring the safety and the effectiveness of biological products, including biosimilar therapeutic protein products.