may differ from those involved in another. ADCC may be an active mechanism of action for infliximab in the setting of CD and UC, but not in the setting of the studied RA and AS. Therefore, extrapolation from RA and AS to inflammatory bowel diseases (IBDs) cannot be recommended. For the same biosimilar product, EMA granted all indications. EMA believes that a lower amount of afucosylation species, which translates in a lower binding affinity to FcγRIIIa receptors, is not considered clinically relevant because it does not affect the activities of biosimilar infliximab in the experimental models that are most relevant to the pathophysiological conditions. Furthermore, the contribution of ADCC to the mode of action of infliximab, or any TNF antagonist, has not been established in patients (EMA, 2013).

In order to support extrapolation of indications, additional factors that may influence the decision to allow extrapolation have to be considered (Scott et al., 2014). The studied population (age, sex, and ethnic origin, etc.) should be similar to and representative for those being extrapolated. The primary clinical trial's duration of treatment, route of administration, and dosage range should be similar: extrapolation to a different route (IV to SC) or from a low dosage to a high dosage would unlikely be permissible if there is no PK/PD bridging study. Similarly, extrapolation between two indications with very different immunogenic profiles would not be likely. Monotherapy is recommended to support extrapolation of indications, if a well-established monotherapy has been used by the originator's product in a population that is considered to be sensitive to detect differences and is representative of the target populations intended for clinical practice. Since monotherapy would provide better comparative efficacy, safety, and immunogenicity profiles without the interference of concomitant medications, biosimilar sponsors should make an effort to select such a patient population that allows for comparison and extrapolation.

In general, extrapolation is based on the totality of evidence that could be scientifically verifiable and rationalized; uncertainty that may cause efficacy and safety concerns needs to be addressed prior to marketing authorization of biosimilars; and if similarity cannot be sufficiently demonstrated, sponsors should pursue a standalone authorization pathway.

In order to extrapolate the data generated with a biosimilar in one indication to other indications held by the RBD, it will be critical to design and conduct a high-quality equivalence trial with carefully selected equivalence margins. The trial should be shown to have assay sensitivity, and there should be some confidence that the constancy assumption is valid in order to facilitate in the proper interpretation of the trial results.

9.4 STATISTICAL CONSIDERATIONS

9.4.1 Designing a Meaningful Trial to Support Additional Indications

Although equivalence or noninferiority studies may be acceptable for the comparative clinical studies of the biosimilar to the RBD, equivalence trials are generally preferred (Health Canada, 2010; WHO, 2010; EMA, 2015; FDA, 2015). A demonstration of equivalence, as opposed to noninferiority, is especially important when extrapolation to other indications is one of the goals of the development program for