markers be added to the PK studies whenever possible. These markers should be selected based on their clinical significance.

Although efficacy comparative studies are usually required, in some cases, PK/PD comparative studies with the biosimilar medicinal product and the reference may be sufficient to demonstrate clinical comparability if there is a clearly demonstrated dose response and the PD marker is an accepted surrogate marker linked to clinical efficacy. Therefore, demonstrating a similar effect on the PD marker ensures a similar effect on clinical outcome. Examples of such markers are the ANC (absolute neutrophil count) to evaluate the effect of granulocyte-colony stimulating factor (G-CSF) or reducing early viral load in chronic hepatitis C to evaluate the effect of alpha interferon.

If surrogate markers for efficacy are not available, it is usually necessary to demonstrate comparable clinical efficacy between the biosimilar and the reference product by adequately powered, randomized, parallel-group comparative clinical trial(s), preferably double-blind, by using efficacy endpoints. The study population should be representative of the therapeutic indication(s) authorized for the reference product and should be sensitive to detect differences between this and the biosimilar. Occasionally, changes in clinical practice may require deviation from an approved therapeutic indication, for example, due to concomitant medication, line of therapy, or the severity of the disease. These deviations should be adequately justified and discussed with regulatory authorities. Generally, the trial design should be performed to demonstrate equivalence. The purpose of the efficacy trials is to detect a clinically significant difference between the reference product and the biosimilar. Clinical comparability margins should be prespecified and justified on both statistical and clinical grounds by using the data from the reference product.

Clinical safety is important throughout the clinical development program of the biosimilar, and comparative data should be obtained from the PK/PD studies and also as part of the clinical efficacy study. Normally, comparative safety data should be collected before the marketing authorization considering the type and severity of the safety problems described for the reference product. The safety assessment continues throughout the commercial life of the biosimilar medicinal product, in the same way as for any other biological medicine.

Evaluation of immunogenicity of the biosimilar in comparison with the reference product should be conducted by using the same assay format and sampling scheme. The duration of immunogenicity study should be justified, depending on the duration of the treatment course, disappearance of the product from the circulation (to avoid interference in the assays), and the time when a humoral immune response develops. The type and amount of immunogenicity data will depend on the experience gained with the reference product and the product class.

15.3.3.3 Extrapolation of Indications

If the reference medicinal product has more than one therapeutic indication, the extrapolation of the efficacy and safety profile of the biosimilar to other indications not studied during the clinical development could be acceptable but needs to be scientifically justified. The justification should consider all the comparability data gathered (i.e., quality, nonclinical, and clinical) and will depend on the clinical