experience with the medicinal product, available bibliographic data, knowledge of the mechanism of action of the active ingredient, and the receptors involved for each indication. If there is evidence that different active sites of the reference medicine or different receptors on target cells are involved in the different therapeutic indications, or that the safety profile of the product differs between them, additional data may be required to justify extrapolating the safety and efficacy from the studied indication in pivotal clinical trials. The final decision will be based on the evidence from all the comparability studies and the assessment of any possible uncertainties that may remain.

This still remains one of the most controversial issues regarding the acceptance of biosimilars and is discussed in more detail below.

The extrapolation of indications is discussed in greater detail in Chapter 9 of this book and under 15.5 below.

15.3.3.4 Pharmacovigilance

It is acknowledged that data derived from preauthorization clinical studies with the biosimilar are usually insufficient to identify rare adverse effects. Therefore, clinical safety of biosimilars should continue to be monitored after the marketing authorization.

The applicant should provide a description of the pharmacovigilance system and a risk management plan in accordance with the existing EU legislation. The risk management plan should consider the identified and potential risks associated with use of the reference product and, if applicable, possible additional risks identified during the development program of the biosimilar. The plan should also detail how these issues will be addressed in the postmarketing period. Immunogenicity should also be addressed in this context. Any specific safety measures imposed on the reference medicinal product or therapeutic class should be taken into consideration. Traceability is a critical aspect for the pharmacovigilance of biological medicines in general; therefore, it is not different for authorized biosimilar medicines. The identification and reporting of any adverse reaction require the information reporting the brand name and specific batch number of the concerned product.

Pharmacovigilance for biosimilars is discussed in greater detail in Chapter 13 of this book.

15.3.4 Product-Specific Guidance

In addition to the general considerations previously described for nonclinical and clinical comparability studies, specific additional requirements have been developed for certain biosimilar medicinal products such as human somatropin, erythropoietin, insulin, G-CSF, alpha interferon, low-molecular-weight heparin, monoclonal antibodies, follicle stimulating hormone (FSH), and interferon beta (EMA website). The characteristics and type of nonclinical (toxicological and pharmacological) and clinical studies (PK, PD, safety, and efficacy) are described in these annexes for each drug class considered. Clinical aspects such as the study population, design of clinical studies, and the possibility of extrapolating clinical indications from the reference medicine are discussed. Immunogenicity data needed for the approval of each type