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# Preface

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The last few decades have seen a rapid rise in novel drugs that mimic the compounds found in the body, such as peptides, proteins, oligonucleotides, certain therapeutic vaccines and genes. These products, especially when derived from biotechnological processing, are commonly referred to as “biopharmaceuticals”, although the classification as biopharmaceuticals differs slightly between Europe and the USA. Currently, these compounds constitute about 50% of all new drugs in pre-clinical development and about 25–30% of all new approved drugs.

Biopharmaceuticals are strikingly different from low molecular weight drugs. Their delicate and complex nature, as well as their poor absorption through biological membranes, renders them a tough challenge for the scientist that wants to develop a rugged therapeutic for the market. As a result, delivery of these compounds is usually by injection or infusion, and the formulation is often unique for each new biopharmaceutical. Some of the analytical and formulation challenges of biopharmaceuticals have been addressed in two previous volumes in these series (volume II: *Lyophilization of Biopharmaceuticals* and volume III: *Methods for Structural Analysis of Protein Pharmaceuticals*).

Biopharmaceuticals also introduce another challenge, usually absent for low molecular weight drugs, which is the ability to provoke an unwanted immune response. This immune response not only can reduce the effectiveness of the therapy, but can also lead to serious and life-threatening side-effects. Most biopharmaceuticals are to some extent immunogenic, and as a result the regulatory agencies insist that for protein pharmaceuticals potential antidrug antibody formation is studied during drug development.

As many patents are expiring for first-generation biopharmaceuticals, biogeneric products (also termed biosimilars) are approaching the market. The risk of an immune response is a major concern in development of these biosimilars, especially since biopharmaceuticals are often too complex to characterize in full detail. Minor differences between two products may, however, lead to a big difference in immunogenicity, which may not be picked up in small clinical trials of short duration.

The focus of this book is this potential unwanted immune response to biopharmaceuticals. The book is essentially divided into three parts: The first five chapters give a general overview of the nature, causes and (clinical) implications of immunogenicity of biopharmaceuticals, as well as of the prediction and analysis of immunogenicity. The next six chapters present specific cases of immune responses to biopharmaceuticals. The final chapter contains a

discussion on risk management of potential unwanted immunogenicity during the drug development process.

The reader will note that the primary focus in all but one chapter is on unwanted immunogenicity of protein pharmaceuticals. This is due to the fact that these constitute the vast majority of biopharmaceutical products and that experience with other biopharmaceuticals is very limited. However, we believe that the concepts discussed in this book will be valid for non-protein biopharmaceuticals also.

Regrettably, this book cannot give a definite answer to the question what factors cause unwanted immunogenicity, and what to do about it. Our insights into many of the mechanisms are still too limited to provide a clear answer. However, the book outlines the present state of knowledge and provides some potential explanations and caveats.

The book should assist those working in early drug development of biopharmaceuticals and allow them to define potential areas of concern as early as possible. It will also serve the formulation scientist, who is responsible for preparing a stable and safe product. Awareness of some of the risk factors for immunogenicity development can aid in preventing future failure of the product. Pharmacologists and clinicians working with biopharmaceuticals may also benefit from this book, as it gives potential explanations for several observations and provides discussions on the methodology used to determine and quantify the immune response. Finally, the book will be of interest to academics, from M.Sc. upwards, working with biopharmaceuticals. It shows that there is still much to learn in this area, and it contains a number of warnings for those developing novel biopharmaceuticals and advanced drug delivery systems.

The editors hope that this book will contribute to the development of better and safer biopharmaceuticals. We also hope that this book can promote a concerted effort in elucidating the important risk factors that lead to immunogenicity.

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