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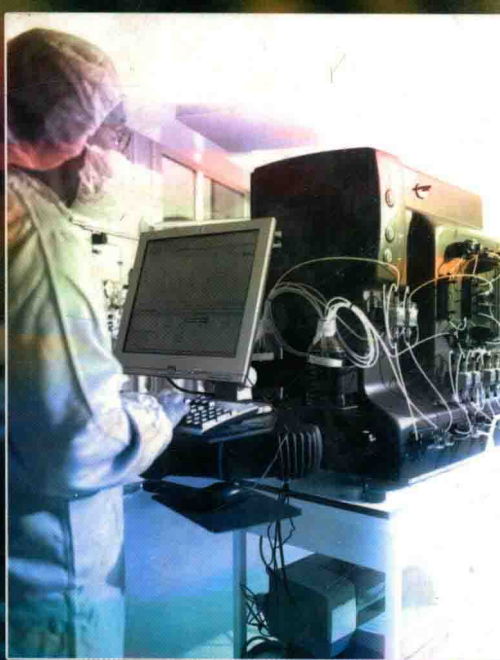
Second Edition

Handbook of Process Chromatography

Development, Manufacturing, Validation and Economics



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Preface

Biotherapeutics have become the main drivers for the pipeline of the pharmaceutical industry, and carry hope for millions of patients for a better life with, or even cure from, diseases for which there are no existing effective treatments. This group of medicines includes, but is not limited to, protein and nucleic acid-based therapeutics as well as different classes of vaccines and gene therapy treatments. Today, there are a few hundred licensed biotherapeutics produced from genetically engineered cells and over a thousand are in pre-clinical and clinical studies.

Process chromatography provides companies developing or manufacturing biological pharmaceuticals tools to fulfil high requirements on safety and quality of active ingredients. This book discusses process chromatography tools and their capabilities; and it does so with all the main interrelations between different phases of manufacturing kept in mind.

Since the first edition of this book, the field has matured significantly and has seen a number of important new aspects in business strategies, manufacturing framework and use of new technology. Emphasis has shifted away from the focus on individual steps and their technical performance to a more comprehensive process operational view. Statistical tools are now used to establish robust operating parameters, and analytical methods have been significantly improved.

In this book, we take a holistic approach to describe purification processes by considering the biopharmaceutical industry and its needs, the types of products and the sources from which they are produced, other technologies that are used prior to purification and some other technologies, such as filtration that complement chromatography, which is still the workhorse of downstream purification.

In Chapter 1, we address the state of the biopharmaceutical industry today. This sets the stage for the subsequent chapters. Much has changed. For example, the whole concept of follow-on products, generic approaches and platform technologies were not even topics of interest when the first edition of this book was published.

Chapter 2 describes process capability from the perspective of several functional departments, the market needs for biopharmaceuticals and some production setups for manufacturing at different scales during the various stages of development and production. The ability of mammalian cell and microbial substrates to meet the future market demands is explored, and the use of multi-product facilities described.

Chapter 3 presents process design concepts that enable development of a process suitable for manufacturing biotherapeutics. We discuss, among other topics, the importance of risk assessments, the design of a logical purification strategy and characterization studies. Expression systems used to produce biopharmaceuticals, with an emphasis on the most commonly used hosts, *E. coli* and CHO, are discussed in terms of productivity and types of products made today.

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Separation technologies that are discussed in Chapter 4 include both chromatography and filtration. An overview of currently used recovery steps is followed by a discussion on basic chromatography techniques and their optimization and scale-up.

In Chapter 5, in-process and final product analytical methods are presented. Specific analytical tools applied to monoclonal antibodies and nucleic acid products, such as DNA plasmids, are described. Process analytical technologies (PAT), method validation, setting specifications and the use of standards are also addressed.

Chapter 6 addresses the always-important issues of cleaning and sanitization of chromatography resins, reusable filters and equipment. This chapter is followed by validation (Chapter 7), which includes cleaning validation for chromatography columns.

An appendix to the Chapter 7 provides a summary of activities from pre-clinical to post-licensure for biopharmaceutical production from genetically engineered mammalian cells. Current validation trends, which are discussed, may influence future validation costs.

Economy of production has become more and more important since our previous edition. The economics is addressed in Chapter 8.

Chapter 9 on basic properties of biological molecules has been updated to include viral and DNA-based therapeutics and highlights properties of some important type of biopharmaceuticals.

Chapter 10 discusses optimization of separation processes based on well-established chromatography theory. Influence of experimental parameters may be simulated with the software tutorials supplied on a CD-ROM.

Our final two chapters address chromatographic equipment and column packing. New equipment designs, improved automation and pack-in-place columns are discussed.

Appendices with detailed references for nomenclature of liquid chromatography, reduced numbers used in process engineering, validation activities during development and the simulation tutorial complete the content of the second edition of *Handbook of Process Chromatography*.

We hope you will find the content of this book helpful for your daily work and as your reference in the coming decade.

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Biopharmaceuticals Today

1.1 INDUSTRIAL CONTEXT

In our introduction to the 1st edition of this book in 1997 we wrote: 'In the rush to get a product to market, process optimization and validation are often sacrificed', which indicated a certain lack of maturity in the biopharmaceutical field at that time. Those days are gone. A significant portion of biopharmaceutical drug development is now performed by experienced big pharma and a small number of established biopharma companies. In addition, there are hundreds of small companies and start-up institutions without sufficient competence to bring novel biopharmaceuticals all the way to market; but today, even these organizations have full access to the required expertise from contract manufacturing and clinical research organizations.

Consequently, the routines followed by this industry have matured. Where there was once mere science and many remaining unknown issues for manufacturing protein-based drugs, there are now sets of tools, the challenges are well understood and relevant information is in the public domain. Process chromatography, the main topic of this handbook, is one of the most important tools due to its close relation to end-product quality and safety. Well-managed platforms with overall workflow and specific methods are being established for every aspect of process development, analytical tasks and even regulatory procedures. These platforms are upgraded in a carefully controlled fashion following progress in science and applicable technology. Knowledge gaps are closing rapidly.

In addition to biochemical and biological science, process engineering is beginning to dominate the field as protein production loses most of the 'mysteries of biology' and moves towards predictable and controllable production operations. This is not, yet, the situation with emerging gene and cell-based candidate therapeutic agents, where the uncertainties and inexperience reflect the situation that existed for protein drugs just two decades ago. The design of work strategies and methods for these novel medicines still constitutes a major challenge for their developers, as well as for regulators evaluating the associated risks.

The following sections in this chapter provide a brief history and describe the current biopharmaceutical business. Our description is qualitative, i.e. where there are business-related numbers, they are merely intended to create a snapshot that may help to illustrate or exemplify our points. We are perfectly aware that this industry is moving too fast to

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