

# Quality for Biologics

***Critical quality attributes, process and change control, product variation, characterisation, impurities and regulatory concerns***

## Table of Contents

### Part One: Manufacturing Considerations for Ensuring Product Quality throughout the Life Cycle

#### Chapter 1

##### What Controls the Quality of a Biologic?

**Alain Bernard PhD, *Vice President, Global Process Development & Industrialization, UCB Group, Belgium***

**Dr Stefanos Grammatikos MSc PhD, *Senior Director, Biological Process Development & Industrialization, UCB Group, Belgium***

1. Introduction
2. Critical quality attributes: Aspects of a biological that may impact function and safety
3. Impact of the process on the product
4. Setting the specifications
5. Comparability, product lifecycle management and regulatory guidelines
6. Regulatory perspectives
7. Conclusions

#### Chapter 2

##### Process Development and Technical Stewardship through the Lifecycle of APIs Manufactured by Cell Culture/Fermentation

**Graham McCartney PhD, *Technical Lead Biotechnology, Eli Lilly, Ireland***

1. Introduction
2. The importance of process understanding and process validation
3. Value of generic platforms for manufacturing processes
4. Viral clearance requirements

## **Chapter 3**

### **Process Analytical Technology (PAT): Application in Manufacturing of Biologics**

**Anurag S. Rathore PhD, *Research Scientist, Process Development, Amgen Inc., USA***

1. Introduction
2. Regulatory guidance
3. Approaches and applications
4. Summary including pitfalls of implementation of PAT in manufacturing

## **Part Two: Characterization and Analytical Methods**

### **Chapter 4**

#### **Introduction: Characterization of the Biologic Product**

**Thomas Schreitmueller PhD, *Head of Analytical R&D and Quality Control Biotech Products, F. Hoffmann-La Roche, Switzerland***

1. The historical perspective
2. The current status
3. The perspective
4. Some examples
5. Conclusions

### **Chapter 5**

#### **Technology Selection for Physicochemical Characterisation**

**Dr John O'Hara, *Characterisation Group Leader, Analytical Research and Development, UCB-Celltech, UK***

**Dr Andy Hooker, *Senior Director of Analytical Research and Development, UCB-Celltech, UK***

1. Introduction
2. Well characterised biologicals and specified biotechnology products
3. Heterogeneity of biopharmaceutical products and physicochemical testing
4. Evolution in physicochemical characterisation during development
5. Physicochemical characterisation and bioactivity
6. Physicochemical lot release testing
7. Case studies

## Chapter 6

### Bioassays for Lot Release and Comparability

**C. Jane Robinson PhD *Principal Scientist, Biotherapeutics, National Institute for Biological Standards and Control, UK***

1. Introduction
2. Biological activity, potency, functional assays
3. Selection of appropriate bioassay systems
4. Types of functional bioassay system
5. Binding assays
6. Immunoassays
7. Bioassays and unwanted immunogenicity
8. Assay variability, reference standards and relative potency
9. Assay Design
10. Assay precision
11. Surrogate potency assays

## Chapter 7

### Impact of Formulation Design on Stability and Quality

**Patrick Garidel PhD**

**Stefan Bassarab PhD**

***Department of Process Science, Formulation Development, Boehringer Ingelheim GmbH, Germany***

1. Introduction
2. Stability issues with biologics
3. Liquid versus dry dosage forms
4. Stability testing and quality criteria of drug substance and drug product
5. Conclusions

## Chapter 8

### Specifications and Drug Substance for Lot Release

**Siegfried Schmitt PhD MRSC CChem CSci, *Principal Consultant, Parexel Consulting, UK***  
**Ralf Hess MSc PhD, *Principal Consultant, Parexel Consulting, Germany***

1. EU and US perspectives on setting specifications
2. Setting the specifications (acceptance criteria) and the action limits (critical product quality attributes) for quality control for specific products
3. How specification requirements tighten during development and how to update the package
4. How design space helps with the determination of specifications, especially for generic products outside the originator product specifications
5. Parametric release, i.e. real-time product release
6. Methodologies that need validation

## Part Three: Impurity Profiles and Product Variation

### Chapter 9

#### Impurity Profile: How the Process can Impact on the Impurity Profile, and Characterisation of Product and Process Related Impurities

**Stefan Zietze MSc PhD, *Head of Quality Control,***  
**Marco Riedel PhD, *Director of Q A, Qualified Person,***  
**ProBioGen, Berlin, Germany**

1. Nature of product- and process-related impurities
2. Characterization of product- and process-related impurities
3. Impact of impurities on product quality

### Chapter 10

#### Impact of the Process on Aggregation, and Technologies for Aggregation Analysis

**Professor Nigel Jenkins, *Principal Investigator,* National Institute of Bioprocessing Research and Training (NIBRT), University College Dublin, Ireland**  
**Dr Ray Tyther, *Senior Scientist,* NIBRT Laboratory, National Institute for Cellular Biotechnology (NICB), Dublin City University, Ireland**  
**Dr Lisa Murphy, *Senior Scientist,* NIBRT Laboratory, National Institute for Cellular Biotechnology (NICB), Dublin City University, Ireland**

1. Introduction
2. Interventions in the protein secretory pathway
3. Disulphide bond formation
4. Chaperones
5. Multiple gene activators
6. Environmental conditions
7. Analytical methods to detect misfolding and aggregation
8. Conclusions

### Chapter 11

#### Importance of Non-Clinical Testing

**Nadja Prang-Richard PhD MBA, *Program Director for Monoclonal Antibodies,* LFB, France and *Co-Founder & Scientific Advisory Board Member,* Lophius, Biosciences, Germany**

1. Introduction
2. Regulatory aspects
3. In vitro systems
4. In vivo systems
5. Pharmacokinetics
6. Toxicology studies
7. Non-clinical testing in (BIO)pharmaceutical development

# Part Four: Regulatory Considerations Regarding Product Quality

## Chapter 12

### Current Safety and Efficacy Concerns of the Regulatory Authorities

**Frits Lekkerkerker MD, *Former CHMP Member and Chairman, Medicines Evaluation Board, Netherlands, Member Advisory Board, NDA Regulatory Science Ltd***

1. History
2. New regulatory guidance
3. Expectations of the regulatory authorities
4. Where the industry tends to go wrong
5. Will biologicals become harder to regulate?

## Chapter 13

### Requirements for an Effective CMC Regulatory Compliance Strategy

**Steffen Gross, PhD, *Laboratory Head and Scientific Assessor (Quality, Pre-clinic Section Monoclonal and Polyclonal Antibodies, Paul-Ehrlich-Institute, Germany***

1. Introduction
2. CMC requirements for dossier filing
3. Development of a product - interaction with regulatory authorities

## Chapter 14

### Regulatory Considerations in Performing Comparability Studies for Biotechnology Products: An Industry Perspective

**Wassim Nashabeh Ph.D., *Director, CMC Regulatory Affairs,*  
Ron Taticek Ph.D., *Director, CMC Regulatory Affairs,*  
Reed J. Harris, BSc, *Senior Director, Protein Analytical Chemistry*  
Genentech, Inc., USA.**

1. Introduction
2. Definitions and scope
3. General principles

# **Supplement: A QbD Approach to Biopharmaceutical Glycosylation:**

**Dr Daryl Fernandes, Chief Executive, Ludger Ltd**

## **Part 1: Importance of glycosylation to developers and manufacturers of glycoprotein therapeutics**

1. Introduction
2. Why measure quality of biopharmaceutical glycosylation?
3. Glycosylation and risk in biopharmaceutical production
4. Steps for setting up a glycosylation quality system

## **Part 2 – Glycoprofiles and Glycoprofiling**

1. Introduction
2. Monosaccharide profiling
3. Oligosaccharide profiling
4. Glycosylation site profile
5. Glycoform profile
6. Glycoprofiling throughout the drug life cycle
7. Conclusions

## **About the Contributors**