

Quality for Biologics

This report will appeal to producers of innovator biological products and to biosimilars, to large and small biotech, and to large pharma with current interests in biologics or wishing to increase their portfolios to include biologics. In particular it will appeal to those investigating product and process development, analytical development and characterisation, product quality, non-clinical, pre-clinical and clinical development, and regulatory affairs. The report covers non-vaccine biologics such as therapeutic proteins including antibodies, cytokines and enzymes.

Biologic drugs are complicated biological products that are mostly difficult to define in molecular terms and that can be inconsistent in their exact composition. This leads to difficulties in the assurance of product quality in terms of safety and efficacy. There is no perfect solution, hence the need for this report. The commercial cost of quality is great for getting it right but can be considerably greater or even disastrous for getting it wrong. Considerable time and expense can be saved by having an educated approach to manufacturing and process development, characterisation and analytical methods, product variation and also to regulatory issues.

Part One: Manufacturing considerations for ensuring product quality throughout the life cycle

Critical quality attributes, manufacturing process parameters, and process analytical technology

To ensure product quality of the biologic in terms of safety and efficacy the investigator needs to understand, define and control the critical quality attributes of the product. Biologics are subject to variability and thus critical product quality parameters, process parameters and associated acceptance criteria need to be selected. This first chapter in this report examines the product features that can impact on quality attributes. The authors explain when critical quality attributes are measured and how product attributes can change with time. The investigator must be constantly on the alert as despite extensive testing, side effects leading to safety warnings and expensive further studies can occur. Examples are provided.

Dilemmas exist such as the difficult decision of whether to invest heavily in product and process characterisation at an early stage or to wait until the market success of the product can be better assessed. Additionally, exact setting of specifications relating to safety and efficacy is impossible at the start and has to allow sufficient range to accommodate results from the later experience.

Here and throughout the report there is emphasis on the concepts of “design space” and process understanding leading to Quality by Design which is meant to cope with variability and deliver a consistently high quality product.

Additionally, this first chapter serves as an introduction to the entire report with mention made of all the important features including: the impact of the

process and cell line, impurities, aggregation, post-translational modifications, physicochemical characterisation, functional testing, glycosylation and the setting of specifications.

The second chapter provides in-depth advice on manufacturing of the product over the entire product lifecycle to ensure constant product quality. Emphasis is placed on the importance of process understanding based on meaningful and targeted but not excessive experimentation. An explanation is provided on how process development involves prioritization of quality attributes and how this can be used to drive the next phase of development work. Subsequent process validation is important to demonstrate that the process can perform consistently in production scale to produce batches of the required quality. The chapter describes how validation is no longer a one time exercise but must now incorporate a strong element of continuous improvement.

Readers of the report will want to find out how the experts minimise the impact of the process on the product and in particular how they develop manufacturing platforms with quality in mind. These platform technologies are designed to align discovery to development to commercial manufacturing. The biotech organisation will need to structure teams and reassess their documentation and project management approach. The challenges, the flexibility required and the limitations to this approach are discussed. In addition, this chapter also outlines the relevance and importance of robustness of viral removal studies for controlling the risk of viral contamination.

The third chapter examines the application of process analytical technology (PAT). This has the potential for continuous quality assurance resulting in improved operational control and compliance and ultimately reliable final product quality. A desired goal of the PAT framework is to design and develop well-understood processes that will consistently ensure a predefined quality at the end of the manufacturing process. This technology has worked well in other industries. This chapter outlines the status quo of where the biologics industry stands with the implementation of PAT and how this is likely to evolve in near future.

Part Two: Characterisation and Analytical Methods

Physicochemical analysis, bioassays, formulation and specifications

Chapter 4: Introduction

Determination of the critical quality attributes and maintenance of product quality are of course dependent on application of a variety of characterisation and analytical technologies. Those responsible for characterisation need to test for all the permutations and to determine an acceptable level of variation for setting the product specifications. Assays need to be developed and validated so that an analytical protocol can be set in place for an individual product, although it must be borne in mind that this protocol will change as the product develops. Analytical testing is required for impurities, aggregation, post-translational modifications, physicochemical characterisation, and

functional activity. Ultimately these results need to be correlated with biological testing and with non-clinical and clinical studies.

Characterization needs change during the development of a product. The investigator needs to know how to work out a protocol starting with a generic set of assays and methodologies and to optimise them to make them product specific. In the fourth chapter, a number of analytical technologies are examined in terms of their applicability, their ease/difficulty of use and their limitations, the time, and the investment and experience required to develop them.

Physicochemical characterisation, outlined in chapter 5, requires the selection of analytical technologies that are quantitative, specific and sensitive. As products and heterogeneity become more diverse, there is increasing use of more advanced technologies. This chapter on technology selection for physicochemical characterisation outlines the various types of product variant. It stresses the importance of understanding the heterogeneity of the product and explains how this can form part of the product profile. It describes the technologies available for examining different features, for example primary, secondary and tertiary structures, post-translational modifications and biological activity. Furthermore, this chapter looks in detail at the characterisation requirements at different stages of development ranging from clonal selection until post-marketing process changes and its application for forced degradation studies and lot release testing. It makes clear the advantages of developing these studies as early as possible in the product life-cycle.

In addition to the previously-mentioned physicochemical characterisation, a selection of bioassays needs to be set up. These are described in chapter 6. For the majority of biologicals, bioassays play an essential role in product development, routine monitoring, stability studies, lot release and comparability. A practical approach to functional assays (comprising animal studies, cell-based assays and/or biochemical ones) is outlined in terms of assay variability, reference standards, and relative potency, together with assay design. Methods are assessed in terms of ease of applicability, expertise required, cost, time required etc. In addition, binding assays and immunoassays, although not necessarily functional assays, are described as they often form part of a functional assay system. The extremely important immunogenicity binding assays to detect and quantify antibodies, and functional bioassays to assess their neutralizing capacity are described in detail in another report of this series.

Chapter 7 covers important features to consider for formulation and stability regarding quality of the product. The ICH Q6B note for guidance on specifications of both drug substance and drug product provides information on general principles for the selection of test procedures and the setting and justification of acceptance criteria for biotechnological and biological products. These are based on physicochemical, biological and/or immunological test procedures to define appearance and description, identity, purity and

impurities, potency and quantity. Chapter 8 provides advice on setting the specifications throughout development and explains how design space can help with the determination of specifications, especially for generic products. Guidance on real-time product release and methodologies that require validation is also given.

Part three: Impurity Profiles and Product Variation

Product- and process-related impurities, aggregation and non-clinical testing

The investigator requires a good knowledge of the nature of both the process-related impurities and the product-related ones and an understanding of the impact these can have on product quality. The purity of a biological product is difficult to determine and depends on the methods applied. Consequently, a combination of methods has to be applied. Chapter 9 provides examples of both product-related impurities and process-related ones together with detailed examples of the many available technologies for their identification and quantification. The importance of ensuring both anticipated and non-anticipated impurities are picked up is emphasised.

Protein aggregation can occur at all stages of manufacturing and, in the case of recombinant proteins, must be prevented or eliminated in order to avoid immunogenicity or problems at the site of drug administration. Chapter 10 of this report examines the molecular mechanisms of aggregation and describes how aggregation impacts on the product. A wide spectrum of analytical technologies is presented and examined in terms of cost, speed, ease of applicability and robustness. These are evaluated in terms of pros and cons with suggestions for overcoming any drawbacks. In addition, the chapter outlines the causes of aggregation and provides details of various strategies being evaluated to combat aggregation and misfolding in upstream and downstream processing.

The importance of non-clinical testing of biopharmaceuticals has been emphasised by the recent incident during a phase I clinical study with TGN1412, an anti-CD28 monoclonal antibody, which caused adverse reactions in all six healthy volunteers. As a result the regulatory authorities have introduced a new guideline with increased scope which includes additional risk assessment, comparability studies, animal and pre-clinical studies and re-design of phase one clinical testing.

The application of optimal non-clinical safety and efficacy evaluation can improve predictive value, identify undesired adverse reactions, shorten the time and cost of launching new pharmaceuticals, and speed up time to market. The chapter on non-clinical testing (chapter 11) focuses on the assessments that accompany discovery, pre-clinical and clinical development, and also the post-marketing period. It examines current practices and the implementation of the new guideline, including case-to-case evaluation and risk assessment. Advice is provided on selection of relevant species, safety/toxicity endpoints, and the transition from preclinical to clinical development together with information on current *in vitro* and *in vivo* systems, pharmacokinetics, toxicology studies and non-clinical testing.

Part Four: Regulatory considerations regarding product quality

Regulatory authority expectations, risk management and comparability concerns

The changes to the manufacturing process frequently introduced during the development of a biological necessitate a more thorough regulatory evaluation compared with ordinary chemical substances. Over the years concept papers and guidances have been issued together with regulatory evaluation resulting in the release of the ICH Q5E document. This became necessary after the introduction of biosimilars and even more so after the incidence of pure red cell aplasia resulting from administration of one batch of a biosimilar version of epoietin. More recently, the CHMP biosimilar working party has prepared guidance for the industry and for the assessors on the comparability requirements and their evaluation.

Chapter 12, which deals with current regulatory concerns on safety and efficacy, outlines the expectations of the regulatory authorities in terms of comparability, non-clinical, clinical and immunogenicity studies and provides expert advice on risk management plans. The general pitfalls experienced by the industry, for example in terms of their underestimation of the influence of manufacturing change, over-reliance on quality testing, and general difficulties with approach, timing, technology and risk management are all described.

The requirements for an effective CMC compliance strategy are outlined in the next chapter 13. Some features are common to all biologics but not all. The requirements for dossier filing, in terms of the manufacturing process, characterisation and analysis, and stability are all explained. Moreover advice on interaction with the regulatory authorities in terms of clinical trial applications and the seeking of scientific advice is provided.

Finally, in Chapter 14, an industry perspective based on extensive experience is presented on comparability exercises to ensure consistent delivery of safe and efficacious product. Advice based on considerable experience is given on lifecycle management, continual improvement, and efficient dealing with the regulators. The chapter gives details on when comparability must be performed and how the exercise depends on the nature of change, the type of molecule and on the stage of clinical development. It examines key technical and regulatory strategic approaches including the type and extent of required analytical, biological and pre-clinical and/or clinical studies, and discusses the setting of associated rationale acceptance criteria.

Supplement on Glycosylation

Biopharmaceutical glycosylation is covered from a quality by design perspective. The first part outlines the importance of glycosylation to developers and manufacturers of glycoprotein therapeutics. Glycosylation of the molecule can be either desired or undesired, and the investigator needs to develop a quality scheme for glycosylation to ensure consistency of the product in terms of safety and efficacy, and for efficient dealings with the regulatory authorities. The development of the regulatory position on

glycosylation safety and efficacy profiles is a much discussed area and the investigator needs to refer to guidelines and guidances. In addition, the investigator needs to understand how control of glycosylation offers commercial benefit by enhancing product potency, reducing manufacturing costs and decreasing risk.

The second part focuses on technologies for glycoprofiling and implementation of a scheme enabling determination of glycosylation critical quality attributes relating to safety, efficacy and consistency of the product. The investigator has a choice of technologies although there are limitations to what can be achieved. This report gives an overview of current procedures with an emphasis on stable, accessible technologies that can be readily transferred into biopharmaceutical R&D and QC labs. It gives advice on glycoprofiling throughout the life-cycle from early stage development, through process optimisation and scale up right through to regulatory submissions and lot release. Glycosylation profiling yields valuable information to support structure-activity relationship studies, regulatory submissions and patent applications.