Biologicals 44 (2016) 291–305

Contents lists available at ScienceDirect

Biologicals

journal homepage: www.elsevier.com/locate/biologicals

Determination of critical quality attributes for monoclonal antibodies using quality by design principles

Nadja Alt [a, *], Taylor Y. Zhang [d], Paul Motchnik [e], Ron Taticek [d], Valerie Quarmby [f], Tilman Schlothauer [b], Hermann Beck [c], Thomas Emrich [b], Reed J. Harris [d]

[a] Pharma Technical Development, Roche Diagnostics GmbH, Nonnenwald 2, 82377 Penzberg, Germany
[b] Pharma Research and Early Development, Roche Innovation Center Munich, Roche Diagnostics GmbH, Nonnenwald 2, 82377 Penzberg, Germany
[c] Pharma Technical Development Biotech Europe, F. Hoffmann-La Roche Ltd, 4070 Basel, Switzerland
[d] Pharma Technical Development, Genentech, South San Francisco, CA 94080, USA
[e] Biologics Quality Control, Genentech, South San Francisco, CA 94080, USA
[f] Research and Early Development, Genentech, South San Francisco, CA 94080 USA

ARTICLE INFO

Article history:
Received 9 June 2016
Accepted 10 June 2016
Available online 25 July 2016

Keywords:
Quality by design
Critical quality attribute
Risk ranking and filtering

ABSTRACT

Quality by design (QbD) is a global regulatory initiative with the goal of enhancing pharmaceutical development through the proactive design of pharmaceutical manufacturing process and controls to consistently deliver the intended performance of the product. The principles of pharmaceutical development relevant to QbD are described in the ICH guidance documents (ICHQ8-11). An integrated set of risk assessments and their related elements developed at Roche/Genentech were designed to provide an overview of product and process knowledge for the production of a recombinant monoclonal antibody. This chapter describes the identification of critical quality attributes (CQAs) as an important first step for QbD development of biopharmaceuticals. A systematic scientific based risk ranking and filtering approach allows a thorough understanding of quality attributes and an assignment of criticality for their impact on drug safety and efficacy. To illustrate the application of the approach and tools, a few examples from monoclonal antibodies are shown. The identification of CQAs is a continuous process and will further drive the structure and function characterization of therapeutic proteins.

1. Introduction

The identification of critical quality attributes (CQAs) is an important step in the development of biopharmaceuticals that depends on a thorough understanding of the potential for quality attributes to affect safety and efficacy. The assessment of CQAs is dependent on the definition of the necessary product attributes for the expected product performance as defined by a quality target product profile (QTPP) and taking other sources of information into consideration (Fig. 1). It is further related to process characterization since all CQAs identified need to be assessed for their variability within the manufacturing process in order to define their acceptance criteria and a sound control strategy.

This chapter describes the risk ranking and filtering approach developed by Roche/Genentech to assess CQAs for monoclonal antibody (mAb) products. This approach has been used in several development and licensing stage submissions, and has been refined since its incorporation in the A-Mab case study [1]. Our methodology considers the impacts of product attributes on bioactivity, pharmacokinetics, immunogenicity risk and safety. An assessment of uncertainty regarding the basis for the impact severity scoring is also applied to determine overall attribute criticality. The CQA assessment tool as developed sets a high bar for declaration of quality attributes as non-CQAs since non-criticality of a QA needs to be actively proven by experimental and clinical data of this or a related molecule or can only be assigned upon well accepted scientific literature. Cut-off criteria for impact ranges were established conservatively as described in detail within this chapter.

This risk ranking and filtering approach can be applied to identify potential CQAs early in product development, enabling refinement during the development period to support a suitable control strategy at the licensing stage. It requires focusing on potential patient impacts, without regard for process capability or

* Corresponding author.
E-mail address: nadja.alt@roche.com (N. Alt).

http://dx.doi.org/10.1016/j.biologicals.2016.06.005
1045-1056/

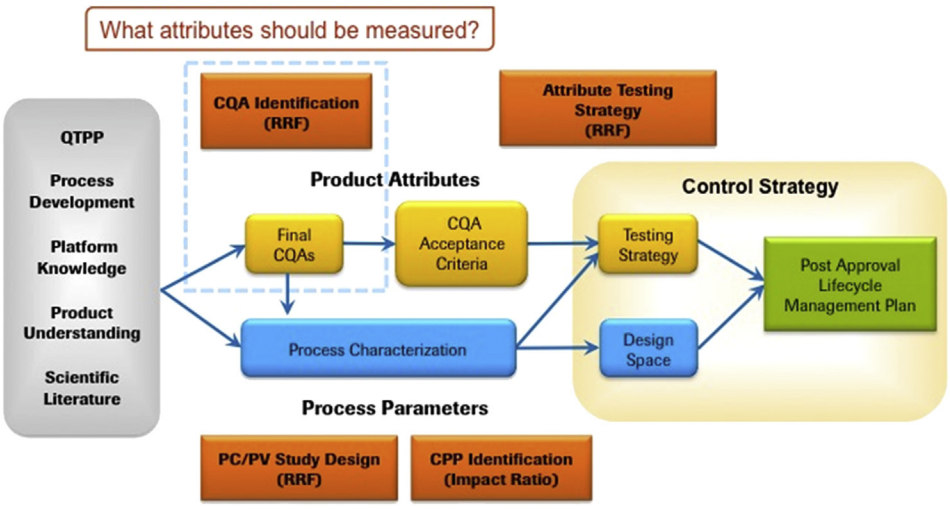

Fig. 1. Quality by design risk assessment tools assess product quality attributes for criticality.

product history, consistent with the definition provided in ICH Q8(R1) [2].

2. Critical quality attributes for monoclonal antibodies

A critical quality attribute is defined in the Quality by Design ICH Q8(R2) guidance document [2] as a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. This definition refers only to potential patient impacts, which allows us to remove process capability from the assessment.

In traditional approaches to pharmaceutical development, quality attributes were assigned to be product-related or process-related substances or impurities, and used to determine specifications (i.e., identify, strength, and purity) that would maintain the analytical profile of the clinical batches. The robustness of the process to deliver the specified product was not the central feature of process design. The more scientific, systematic and comprehensive QbD approach seeks to identify product quality attributes that are critical for the safety and efficacy of the product, thereby building product quality control into the manufacturing process and pharmaceutical dosage form. The QbD tools described below provide design itself, making product testing a risk management activity. This is achieved by a comprehensive and systematic assessment of product variants, process-related impurities, product composition and strength, appearance and microbiological attributes, as well as excipient and raw materials for their criticality.

The pathway towards a final list of CQAs for a mAb is outlined in Fig. 2 and involves several assessment steps starting with the definition of a Quality Target Product Profile (QTPP) which lists the necessary product attributes required to deliver the expected product performance as defined by the target product profile (TPP). The QTPP and additional sources of product quality attribute information are the basis for assembling a list of all potential critical quality attributes (pCQAs).

Quality attributes can be classified in different categories. The list of pCQAs generally comprises product variants and process-related impurities that may potentially impact the molecule's mechanisms of action/mechanisms of toxicity (MoAs/MoTs), or general safety or pharmacokinetic properties. These two categories will be assessed using the risk ranking and filtering approach for CQA identification. While a relationship of each pCQA to clinical outcomes cannot be directly studied, potential patient impact can be inferred from analytical and biological characterization, including structure-function studies. In addition, general product-specific clinical and non-clinical information is gained during product development.

The criticality of pCQAs is assessed using a risk ranking and filtering approach with respect to impact bioactivity, pharmacokinetics (PK)/pharmacodynamics (PD), immunogenicity and safety. Product specific information gained from clinical or non-clinical observations, analytical and biological characterization, studies with related molecules, general (platform) antibody knowledge and published literature are used to complete this assessment.

The identification of pCQAs begins early in development and evolves as more product understanding is gained [3]. Early identification of pCQAs helps to focus development efforts on those attributes where more understanding or control may be needed. The final CQAs are generally confirmed at the later stages of commercial process development in anticipation of the finalization of the commercial control strategy. This systematic approach for identification of CQAs involves a greater analytical effort, but pays off with a deeper understanding of the structure-function relationship of quality attributes and their impacts on product efficacy and safety.

2.1. Definition of a QTPP

The quality profile of biopharmaceutical products, including mAbs, is defined by their Quality Target Product Profiles (QTPP)

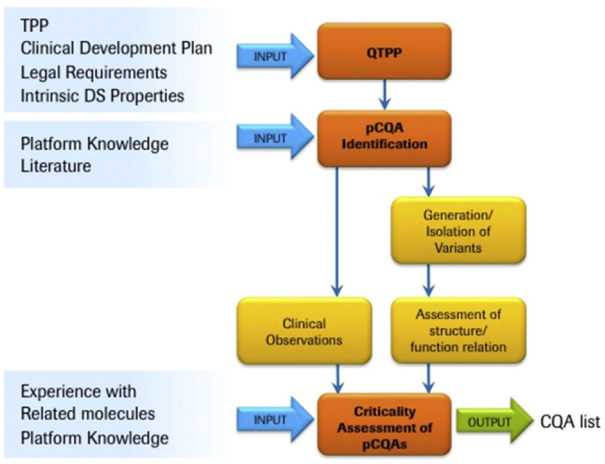

Fig. 2. Outline for workflow for CQA identification.