Journal of Pharmaceutical Sciences xxx (2016) 1–9

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Quality by Design Approaches to Formulation Robustness—An Antibody Case Study

Christine Wurth [1,*], Barthelemy Demeule [2], Hanns-Christian Mahler [1], Michael Adler [1]

[1] Pharmaceutical Development & Supplies, PTD Biologics Europe, F. Hoffmann-La Roche Ltd., Basel, Switzerland
[2] Pharmaceutical & Process Development, Genentech Inc., South San Francisco, California 94080

ARTICLE INFO

Article history:
Received 17 November 2015
Revised 1 February 2016
Accepted 16 February 2016

Keywords:
biotechnology
formulation
HPLC
multivariate analysis
oxidation
factorial design
protein aggregation
protein formulation
proteins
stability

ABSTRACT

The International Conference on Harmonization Q8 (R2) includes a requirement that "Critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can impact the quality of the drug product," that is, the need to assess the robustness of a formulation. In this article, a quality-by-design–based definition of a "robust formulation" for a biopharmaceutical product is proposed and illustrated with a case study. A multivariate formulation robustness study was performed for a selected formulation of a monoclonal antibody to demonstrate acceptable quality at the target composition as well as at the edges of the allowable composition ranges and fulfillment of the end-of-shelf-life stability requirements of 36 months at the intended storage temperature (2°C-8°C). Extrapolation of 24 months' formulation robustness data to end of shelf life showed that the MAb formulation was robust within the claimed formulation composition ranges. Based on this case study, we propose that a formulation can be claimed as "robust" if all drug substance and drug product critical quality attributes remain within their respective end-of-shelf-life critical quality attribute–acceptance criteria throughout the entire claimed formulation composition range.

Introduction

The goal of pharmaceutical development, including formulation and manufacturing process development, is to consistently deliver the intended quality of the product within allowable ranges. Regulatory agencies and industry experts have suggested rigorous approaches to strengthen pharmaceutical development, manufacturing, and quality assurance.[1-3] In August 2002, the Food and Drug Administration launched a new initiative entitled "Pharmaceutical cGMPs for the 21st century: A risk based approach".[4] The aim of this initiative was to introduce innovation into pharmaceutical development. In 2004, the Food and Drug Administration released the Process Analytical Technology Guidance for Industry, which outlined in detail the future expectations of health authorities with regard to developing and implementing effective and efficient innovative approaches in pharmaceutical development.[5] The guidance advocates "building quality into products" by science and risk-based approaches and recognizes statistical experimental design as one of the tools that enable a scientific risk-based approach.

In 2008 and 2009, the International Conference on Harmonization (ICH) guidelines Q8 and Q8(R2) defined quality-by-design (QbD) as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management".[6] These guidelines state that "Critical formulation attributes and process parameters are generally

Abbreviations: AC, acceptance criterion; Buff, buffer concentration; CQA, critical quality attribute; CI, confidence interval; DoE, design of experiments; DP, drug product; EoS, end of shelf life; HMWS, high–molecular weight species; ICH, International Conference of Harmonization; LMWS, low–molecular weight species; MLR, multiple linear regression; Q^2, coefficient of prediction; QbD, quality-by-design; R^2, coefficient of determination; TR, target range.

Conflicts of interest: Medical writing and editorial assistance were provided by Anna Murphy of Fishawack Communications, funded by F. Hoffmann-La Roche Ltd. Christine Wurth, Hanns-Christian Mahler (at the time when the study was performed), and Michael Adler are employees of F. Hoffmann-La Roche Ltd. Barthelemy Demeule is an employee of Genentech Inc.

Current address for Hanns-Christian Mahler: Lonza AG, Drug Product Services, Basel, Switzerland.

This article contains supplementary material available from the authors by request or via the Internet at http://dx.doi.org/10.1016/j.xphs.2016.02.013.

* *Correspondence to:* Christine Wurth (Telephone: +41-61-6889135; Fax: +41-61-6883430).

E-mail address: christine.wurth@roche.com (C. Wurth).

http://dx.doi.org/10.1016/j.xphs.2016.02.013
0022-3549/

identified through an assessment of the extent to which their variation can have impact on the quality of the drug product" and define a design space as "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality". Although design space has primarily been used in the context of pharmaceutical manufacturing processes, it can also be applied to formulation, as confirmed by a question and answers document that was published by the ICH Quality Implementation Working Group in 2011 (Q8/Q9/Q10 Q&A [R4]).[7] The document specifies that "it may be possible to develop a formulation (not component but rather composition) design space consisting of the ranges of excipient amounts and its physicochemical properties (…)" and states that, "the applicant should justify the rationale for establishing the (formulation) design space with respect to quality attributes such as bioequivalence, stability, manufacturing robustness etc." Although intentional movement within a formulation composition design space is not typically desired for a drug product (DP), the goal of pharmaceutical development is to deliver a robust formulation encompassing that product quality is warranted not only at target/label claims for composition but also within permitted ranges of the label composition (accounting, e.g., for manufacturing process-related variations).

This allowed formulation composition range is characterized during development by performing "formulation robustness" studies. The aim of these studies is to select a commercial formulation that is sufficiently robust within the acceptable ranges around the nominal label claim and to meet the shelf life stability requirements, which are typically 24-36 months for pharmaceutical products and at least 18 months at refrigerated conditions (2°C-8°C) for biopharmaceutical DPs.

QbD tools, especially design of experiments (DoEs), have been applied by the pharmaceutical industry to assess and ensure formulation robustness.[8] Examples of formulation robustness studies describing, for example, the effect of excipient composition on process performance can be found in the literature. [9-13] The outcome of such robustness DoE studies can be judged on 2 criteria: (1) Is the resulting regression model statistically significant? (2) Are the output parameters (quality attributes) inside or outside predefined limits? The first criterion, "statistical significance," is routinely assessed when analyzing formulation robustness DoEs by statistical analyses such as multiple linear regression (MLR) methods. To fulfill the second criterion, "acceptable limits" are needed when assessing "robustness."[9-13]

Although this recent literature describes several case studies of formulation robustness, 2 challenges remain: first, the definition and setting of "acceptable limits" are needed to assess formulation robustness with regard to stability until end of shelf life (EoS) within a QbD approach; and second, at the time of market application submission, there are often no EoS stability data available from the robustness study at the intended storage condition. Thus, conclusions with regard to "formulation robustness" are typically based on accelerated temperature and short-term stability testing and are, therefore, more qualitative than quantitative in nature.

For critical quality attributes (CQAs) related to formation of degradant(s) over shelf life, assessment of "acceptable limits" is challenging. Setting acceptable limits for CQAs in a QbD approach for biopharmaceuticals is described in more detail in a series of QbD articles that have been recently submitted for publication.[14-16] In brief, once the CQAs have been identified, an acceptable level or range for each CQA needs to be defined which is called the CQA—acceptance criterion (CQA-AC). The CQA-AC defines the product quality requirement for end of DP shelf life and is set for each CQA based on its potential impact on efficacy, immunogenicity, pharmacokinetics, and patient safety, considering, for example, relevant clinical experience, results from process characterization and validation studies, and clinical data from similar products, including data from literature. The CQA-AC is the sum of all allowed changes for 1 CQA with regard to drug substance (DS) and DP process and stability and can be further divided into allowable ranges for these 4 processing and storage steps, namely for the (1) DS manufacturing process, (2) DS storage ("DS allowable stability range"), (3) DP manufacturing process, and (4) DP storage ("DP allowable stability range"). The limits of each of these 4 process and storage steps are termed CQA target ranges (CQA-TRs). Generally, acceptable limits for process steps are assessed primarily based on characterization and validation data from at-scale data and scale-down models and are further narrowed by a 5% reduction of the derived limit to account for modeling uncertainties. The CQA-TRs for the DS and DP process usually correspond to the DS and DP CQA release specifications, respectively. The DP allowable stability range is calculated as the difference between the DP release specification and the CQA-AC at EoS.

In this case study, the following DP allowable stability ranges were defined based on assessments including product-specific relevant clinical experience, results from process characterization and validation studies, and clinical data from similar products (including data from literature) that are beyond the scope of this article: 13.1 area % for acidic variants, 0.8 area % for high—molecular weight species (HMWS), 1.6 area % for low—molecular weight species (LMWS), and 7.8 area % for oxidized variants. The described DP allowable stability ranges for MAb-A CQAs are very product-specific and need to be determined case by case for each product based on the previously mentioned process.

In principle, formulation robustness can be determined by analyzing the respective quality attributes in real time until EoS is reached. In practice, scientists involved in formulation and DP development wish to obtain an indication of formulation robustness without waiting an unrealistic amount of time. This is comparable to claiming a shelf life for a formulation based on statistical analysis of short-term stability data.[17,18] We propose that this concept may be applied to an entire formulation composition range. Our case study addresses the challenge of how to quantitatively assess formulation robustness for a biotechnology product before real-time EoS data are available by combining concepts of ICH Q8 Pharmaceutical Development ("formulation composition design space") and Q1A(R2) Stability Testing of New Drug Substances and Products ("predicting a shelf life").[6,7,18] Our primary interest with regard to formulation robustness is to guarantee stability of the formulation during storage and until EoS.

Where predefined acceptance limits are available, in general, the following 4 formulation robustness study outcomes can be distinguished: (1) nonsignificant statistical model and all output parameter values (CQA values in our case) are clearly inside predefined limits; (2) significant statistical model and all output parameter values are clearly inside predefined limits; (3) significant statistical model and output parameter values are outside predefined limits; and (4) nonsignificant statistical model and output parameter values are outside predefined limits. The first case provides little knowledge about how formulation factors affect product performance. However, this case represents the ideal outcome of a formulation robustness study because it reflects that the CQA response is not significantly affected by the input (formulation) parameter variations, thus confirming a robust formulation within the predefined limits. The second case also confirms formulation robustness within predefined acceptance criteria. In addition, the statistically significant model would show how formulation factors affect product performance and allows extrapolation according to Q1A if end-of-shelf-life data are not available at time of analysis. The third case provides information on how formulation factors