“Postapproval CMC Changes in the United States with a Focus on Biopharmaceuticals – Current Status and an Outlook in the Pharmaceutical Development”

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List of Abbreviations

ACPS-CP	Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
AR	Annual Report
BLA	Biological License Application
CBE	Change Being Effected
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CMC	Chemistry, Manufacturing and Control
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CTD	Common Technical Dossier
CVER	Center for Veterinary Medicine
DNA	Desoxyribonucleic Acid
DoE	Design of Experiments
EC	Commission of the European Community
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration

FMEA	Failure Modes and Effects Analysis
GMP	Good Manufacturing Practice
HCP	Host Cell Proteins
ICH	International Conference on Harmonisation
KPP	Key Process Parameter
MAA	Marketing Authorisation Application
MAPP	Manual of Policies and Procedures
NDA	New Drug Application
No	Number
NOR	Normal Operating Range
PAR	Proven Acceptable Range
PAS	Prior Approval Supplement
PAT	Process Analytical Technology
PDA	Parenteral Drug Association
Ph. Eur.	European Pharmacopoeia
PhRMA	Pharmaceutical Research and Manufacturers
PHSA	Public Health Service Act
PMP	Postapproval Management Plan
PQR	Product Quality Review
QbD	Quality by Design
QOS	Quality Overall Summary
QTPP	Quality Target Product Profile

RTR	Real Time Release
SOP	Standard Operating Procedure
U.S.	United States
U.S.C	United States Code
USP	United States Pharmacopoeia

1. Introduction

1.1 Definition of Biological Products or Biopharmaceuticals in the United States

According to Public Health Service Act (PHSA) under section § 262 (i) [42 United States Code (U.S.C) 262], the term “biological product” is defined as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. “ [1]

A more specific definition for biological products or biopharmaceuticals can be found on the Food and Drug Administration (FDA) Homepage under Frequently Ask Question. Here they are classified as “a wide range of products such as vaccines, blood and blood components, allergenic agents, somatic cells, gene-based biologics, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism (mainly bacteria, yeast and mammalian cells) and may be produced by biotechnological methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, may be used to treat a variety of medical conditions for which no other treatments are available”. [2]

The Food Drug and Cosmetics Act (FDCA) defines under section § 201 (g) (1) [21 U.S.C 321] “drugs” in general by their function and not by referring to several categories. Drugs are "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals". [3]

It becomes obvious that the definitions of “drugs” and biological products are not mutually exclusive which means that the term “drugs” includes also biological products or biopharmaceuticals. Hence, the FDA regulates biopharmaceuticals as both drugs and biologics because they meet both definitions [6].

1.2 Particularities of Biopharmaceuticals

In contrast to conventional drugs which are mostly small molecules, chemically synthesized with a well-defined and characterised structure, most biopharmaceuticals show a high molecular weight with complex forms that are not easily identified or characterised. Proteins for example, consist of a primary (amino acid sequence), secondary (e.g. structural motifs as alpha helix and beta sheet) and a tertiary (the overall shape of a protein) structure. Sometimes proteins furthermore show a quaternary structure, i.e. that several polypeptide chains (subunits) form a protein complex. Biological products, including those manufactured by biotechnology, are impacted in sometimes unpredictable ways by the manufacturing process, which can cause a change in either potency or immunogenicity [4]. They tend to be sensitive to environmental factors like temperature changes, light, pH changes, shear stress and oxidation. Hence, they are less stable and degrade in more complex ways than conventional drugs. To ensure the maintenance of biological activity and to avoid degradation, stringent conditions for the storage of biological products are necessary [5]. They are also susceptible to microbial contamination like viruses, bacteria, bacterial endotoxins, fungi, yeasts and mycoplasmas depending on their source of origin like the cell line and on the raw materials which are used during the manufacturing process. Therefore, it is necessary to use aseptic principles from initial manufacturing steps, which is also in contrast to most conventional drugs [6]. Another important point is that in a biotechnological manufacturing process it has to be proven that the cell line or cell bank as a biological starting material is able to produce the target product in a consistent and safe way over the whole time of a manufacturing process [7, 8]. This has to be assured by generating an end of production/post production cell line, testing phenotypical or genotypical parameters and/or product quality with respect to stability [7].

Furthermore, a biological product arising from the manufacturing process is often not a pure and homogeneous product. Various isoforms of the molecule are usually present in the medicinal product [6]. According to guideline ICH Q6B three different types of variants are classified for a biological product:

- Product related substances:

  Product related substances are defined as variants of the desired product that

have properties comparable to those of the desired product with respect to activity, efficacy and safety [9].

- Product related impurities:

Product related impurities are classified as degradation products, truncated, oxidised or deamidated forms arising during manufacturing or storage which do not have properties comparable to those of the desired product with respect to activity, efficacy and safety [9].

- Process related impurities:

The third type of variants is process related impurities which are derived from the manufacturing process of biopharmaceuticals. Examples are host cell proteins (HCPs), Desoxyribonucleic Acid (DNA), cell culture media components or leachables/extractables from e.g. chromatography resins or packaging material to be applied in the manufacturing process [9].

These three types of variants have to be taken into consideration during the manufacturing process as they may have impact the final product quality of a biopharmaceutical.

Taking all these points into consideration, it is evident that manufacturing a biopharmaceutical is a complex field with respect to produce a safe and effective drug product as well as to ensure that the manufacturing process continuously delivers product of consistent quality.

1.3 Licensing of Biopharmaceuticals and Conventional Drugs in the United States

Due to all these characteristic features of biopharmaceuticals the regulations for the licensing of biopharmaceuticals differ in comparison to conventional drugs. The United States (U.S.) agency FDA responsible for regulating drugs (both biopharmaceuticals and conventional drugs) approves biopharmaceuticals for marketing through the Biological License Application (BLA) [4, 10]. Conventional drugs are approved through the New Drug Approval (NDA) process [11]. The BLA and NDA are requests for permission to introduce a medicinal product into interstate commerce [12]. The BLA is regulated under 21 Code of Federal Regulation (CFR) §§ 600 - 680 [10, 12]. The NDA is regulated under 21 CFR § 314 [11]. Both application types can be submitted by any legal person or entity who is engaged in manufacture or an applicant for a

license who takes responsibility for compliance with product and establishment standards [12].

The requirements for a BLA and NDA include [12, 13, 14]

- Applicant information
- Product/Manufacturing information
- Data of pre-clinical studies
- Data of clinical studies
- Labelling of medicinal product

In both cases, biopharmaceuticals and conventional drugs, the information described in the BLA or NDA turn into a binding commitment after review and approval of chemistry, manufacturing and control (CMC) processes and procedures by the agency. Meaning that all future batches must be produced according to the regulatory filing so that they meet the quality criteria described in the application [15]. The requirements to show safety and efficacy are similar for a NDA or BLA. The main difference between these two application types is that the FDA requires from the BLA applicant detailed information with respect to the manufacturing process so that the FDA can determine whether the manufacturer is able to consistently produce product under current Good Manufacturing Practices (cGMP) and according to the manufacturing specifications listed in the BLA. Furthermore, the manufacturer´s facility with respect to construction, design, layout, validation processes and environmental monitoring must meet the FDA standards [6]. The agency may also verify the CMC Regulatory Compliance during GMP inspections. If it becomes obvious during a GMP inspection that the applicant deviates from a filed or an approved process or procedure, the resulting product cannot be used in commerce until the applicant has taken the postulated regulatory actions into account [15].

All these requirements are necessary in order to mitigate potential adverse effects on the product quality as changes in the manufacturing process of a medicinal product may have an impact on safety or efficacy. This is especially true for biopharmaceuticals, whose quality as identity, strength, quality, purity or potency and product characteristics are extremely dependent on the manufacturing process.

1.4 Maintenance of Pharmaceutical Product Registrations in the United States

After approval of a pharmaceutical product, the applicant must conduct extensive postmarketing surveillance and maintenance. The main postapproval requirements are:

- Reporting of adverse events
- Manufacturing under cGMP
- Lot release testing
- Postmarketing studies
- Reporting of manufacturing process changes
- Postmarketing reports/Renewal procedure [6].

According to FDA regulations, the applicant is obliged to review and report all of the adverse drug experience information which occurs during e.g. postmarketing clinical investigations, commercial marketing experience and/or postmarketing epidemiological/surveillance studies to the agency [16]. The applicant or manufacturer must report serious, unexpected adverse events within 15 days. Less serious events can be submitted in periodic follow up, distribution reports or in an Annual Report [6, 16]. In principle, the adverse event reporting system in the U.S. does not significantly differ between conventional drugs and biopharmaceuticals [6].

Another important point is that the applicant must show if the medicinal product is manufactured under cGMP conditions. Therefore, the FDA specified standards for manufacturing facilities and production controls. CGMP requirements for biopharmaceuticals were harmonised to be as similar to conventional drugs requirements as possible. However, specific cGMP related regulations for biopharmaceuticals are available [6].

According to e.g. 21 CFR § 610.2, the FDA is able to require applicants or manufacturers to submit samples of a licensed biological product for lot release testing. For this purpose representative samples of each lot must be submitted to the FDA. The lots may not released by the applicant or manufacturer until the agency authorises an “official release” [6, 17].

Furthermore, in some cases the applicant has to commit to the FDA to conduct postapproval clinical phase IV studies in order to maintain the registration of a pharmaceutical product. The reason for conducting clinical trials after approval of a medicinal product is to evaluate whether a medicinal product is safe and effective.

After approval of a medicinal product, it must be guaranteed by the applicant that quality criteria described in the application are not altered [15]. However, during the lifecycle of a product it is likely that changes in the manufacturing process may occur [23, 52]. In these circumstances, the applicant has to prove that the "changed" manufacturing process does not have a negative effect on the safety and efficacy of a medicinal product according to the relevant regulations [21, 22].

The legal basis of manufacturing process changes is given 21 CFR and FDA guidances. The regulations and guidances are separated for biopharmaceuticals and conventional drugs because of the different features. In both cases, it is required to notify the FDA about each change that is related to the "product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established" [21] in an approved license application [21, 22].

Hence, a reporting system was established at FDA which is in general a three-tiered approach. Changes are classified in the U.S. as "minor", "moderate" or "major" based on the risk to the product´s quality, safety, and efficacy according to 21 CFR § 601.12 and § 314.70 [21, 22]. "The FDA must give prior approval before the manufacturer can implement "major" changes." [6] "Moderate" changes must be. reported to the FDA e.g within 30 days in a Change Being Effected (CBE) Supplement and "minor" changes must be reported annually [6, 21, 22].

In the European Union (EU) in contrast, the classification and reporting of a change or variations in the manufacturing system is regulated in the Commission Regulation (Commission of the European Community (EC)) 1234/2008 "Examination of Variations to the Term of Marketing Authorisation for Medicinal Products for Human Use and Veterinary Medicinal Products" [18] and in related EU guidelines. Reporting categories of variations are, classified "depending on their level of risk level of risk to public or animal health and the impact on the quality, safety and efficacy of the medicinal product concerned" [18] which is in principle comparable to the U.S. regulations.

In the EU, the following reporting types are classified:

- Type IA
- Type IB
- Type II
- Extension of a Marketing Authorisation (MAA)
- Urgent Safety Restriction [18].

“Minor” variations are classified in the EU as type IA variation which are reported in an annual report. “Major” variations are graded as type II variation. Type IB variations can neither be categorised as “minor” or “major”. “Extension of a MAA” is a specific type of variation and is listed in detail in Annex I of the Commission Regulation (EC) 1234/2008 [18]. The classification of a variation as “Urgent Safety Restriction” “means an interim change to the product information due to new information having a bearing on the safe use of the medicinal product” [18] in accordance to the Commission Regulation (EC) 1234/2008 [18].

In the EU, a renewal procedure is required in order to maintain an existing MAA. According to the Regulation (EC) 726/2004 of the European Parliament and of the Council which is valid for medicinal products to be authorised by the European Community, “a MAA may be renewed after five years on the basis of a re-evaluation by the Agency of the risk-benefit balance. To this end, the MAA holder shall provide the agency with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the MAA was granted, at least six months before the marketing authorisation ceases to be valid.” [19] Besides, other national renewal procedures exist.

In the U.S. in contrast, a postmarketing report should be compiled. Here, an Annual Report (AR) must submitted according to 21 CFR 314.81 each year within 60 days of the anniversary date of U.S. approval of the application [20]. In the AR, “a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labelling” [20] of the medicinal product are given.

It becomes obvious that, in the U.S. as well as in the EU, maintenance or surveillance after product registration is an essential requirement to assure safety and efficacy of a medicinal product.

The goal of the following sections is to give an understanding with respect to CMC related postapproval manufacturing changes. The focus will be on biopharmaceuticals regulated in the U.S. Furthermore, the current regulatory status and the outlook of the pharmaceutical development will be outlined and discussed in-depth.

2. Managing and Reporting of CMC Changes for Biopharmaceuticals

2.1 General Considerations

As described in section 1.4, if holders of biological license applications (BLAs) need to make postapproval CMC changes to their applications like changes in the production process, quality controls, equipment, facilities, responsible personnel or labelling, they are required to notify the FDA of the details of these changes according to 21 CFR § 601.12 [21] and 314.70 (g) [22]. 21 CFR § 314.70 (g) applies only to "[…] a recombinant DNA-derived protein/polypeptide product or a complex or conjugate of a drug with a monoclonal antibody regulated under the Federal Food, Drug and Cosmetic Act" [22]. Changes to an approved NDA are regulated under 21 CFR § 314.70 (a – f) [22]. Here, it is posted according to 21 CFR § 314.70 (a) that "the applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully." [22]

The applicant needs to provide evidence that no safety and/or efficacy concern is generated by introducing a manufacturing change. Hence, quality data like comparative analytical results of the "pre- and post-change product" (i.e., product batches manufactured prior to and subsequent to a manufacturing change) for the intermediates, drug substances and/or drug products needs to be presented to the agency. However, in some cases it may be impossible or insufficient to describe and assess potential effects of a CMC change only based on a product quality data. In this case the effect of the introduced change also needs to be assessed in non-clinical or clinical studies, in order to show that no negative effect on the safety or efficacy of the product, or on the pharmacological (e.g. pharmacodynamic) and pharmacokinetical properties of the drug product occur [23, 24].

2.2 Process Changes

Process changes are an expected aspect of pharmaceutical manufacturing. Many process changes are a result of increased process knowledge, of an improved manufacturing process or a process scale up, of improving product stability and complying with changes in regulatory requirements during process development and/or postapproval of a medicinal product [23]. When a product is first approved, its manufacturing process represents the current technology standard for manufacturing and follows

the current Good Manufacturing Practices (cGMPs). After approval, market demand, technological advances, changed GMP standards, raw materials sourcing (of e.g. cell culture media, resins etc.) or manufacturing experience may require that the approved process needs to be modified [52]. These points are especially relevant for biopharmaceuticals and need to be addressed in a comparability exercise (see section 2.3.4) [23, 25].

2.3 Regulatory Reporting

For evaluating whether changes in the manufacturing process have a minor, moderate or a substantial effect on the product quality and for evaluating whether this may impact the safety and efficacy of the product, the FDA needs to be notified. In principle, notifying the FDA about CMC postapproval changes by regulatory reporting can be categorised in three types: Annual Report (AR) (minor changes), Change Being Effected Supplements (CBE) (moderate changes) and Prior Approval Supplement (PAS) (major changes). These reporting categories are applicable for conventional drugs as well as for biopharmaceuticals . As mentioned in section 2.1, changes to an approved application and the related reporting types of conventional drugs are regulated under 21 CFR § 314.70 (a – f) [22]. Changes to an approved application and the related reporting types of biologicals are regulated under 21 CFR § 601.12 [21] and 21 CFR § 314.70 (g) [22]. Furthermore, reporting categories of biopharmaceuticals are handled in more detail in the Guidance for Industry “Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products” [26]. More information related to the reporting categories of conventional drugs can be found in the Guidance for Industry “Changes to an Approved NDA or ANDA” [24] including the Scale Up and Post Approval (SUPAC) guidances that provide also recommendations on reporting categories [24].

The different reporting types are exemplarily described for biopharmaceuticals in the following sections.

2.3.1 Annual Report

In an AR, which is submitted each year within 60 days of the anniversary date of approval of the NDA or BLA, minor postapproval CMC changes in the production process, quality controls, equipment or facilities are documented (see 21 CFR §§ 601.12 (d) and 314.70 (g) (3)) [15, 21, 22]. These changes have a **minimal** potential to

have an adverse effect on the product quality [25]. Examples of CMC changes which can be described in an annual report are listed in the following:

- "Establishment of a new Working Cell Bank derived from a previously approved Master Cell Bank according to a SOP on file in the approved license application." [26]
- "Change in harvesting and/or pooling procedures which does not affect the method of manufacture, recovery, storage conditions, sensitivity of detection of adventitious agents, or production scale." [26]
- "Tightening of specifications for existing reference standards to provide greater assurance of product purity and potency" [26].
- "Addition of time points to the stability protocol." [26]
- "The addition or deletion of an alternate analytical method." [21, 22]
- "Any change made to comply with an official compendium that is consistent with FDA requirements." [21, 22]
- "A change in the size of a container for a solid dosage form, without a change from one container and closure system to another." [21, 22]

2.3.2 Change Being Effected Supplement

In a CBE Supplement moderate postapproval CMC changes in the production process, quality controls, equipment or facilities are described. Such changes have a **moderate** potential to adversely affect the product quality. A CBE Supplement is submitted to the FDA before or concurrently with the distribution of the product made using the change [25]. It can be distinguished between two sorts of CBE Supplements:

CBE Supplement (0):

A CBE Supplement (0) is "[…] usually complete and provides the proper information, and based on assurances that the proposed change has been appropriately submitted […]." [25]. The product can be distributed as soon as the FDA receives the CBE supplement (see 21 CFR §§ 601.12 (c) (5) and 314.70 (g) (2) (v)) [15, 21, 22]. Examples for a CBE Supplement (0) are:

- “Addition of release tests and/or specifications or tightening of specifications for intermediates.” [26]

- “Minor changes in fermentation batch size using the same equipment and resulting in no change in specifications of the bulk or final product.” [26]

CBE Supplement (30):

In contrast to CBE Supplement (0), the CBE Supplement (30) is applied for more critical manufacturing changes with respect to the product quality. Submitting a CBE Supplement (30), the NDA or BLA holder has to wait 30 days from the date of submission before the distribution of the product produced with a changed procedure may begin (see 21 CFR §§ 601.12 (c) (3) and 314.70 (g) (2)) [15, 21, 22]. In the following some examples are described which are categorized as a CBE Supplement (30):

- “Addition of duplicated process chain or unit process, such as a fermentation process or duplicated purification columns, with no change in process parameters.” [26]

- “Manufacture of an additional product in a previously approved multiple product manufacturing area using the same equipment and/or personnel, if there have been no changes to the approved and validated cleaning and changeover procedures and there are no additional containment requirements.” [26]

- “Change in the site of testing from one facility to another (e.g. from a contract lab to the applicant; from an existing contract lab to a new contract lab; from the applicant to a new contract lab).” [26]

- “An increase or decrease in production scale during finishing steps that involves new or different equipment.” [21, 22]

- “Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.” [21, 22]

2.3.3 Prior Approval Supplement

In a Prior Approval Supplement (PAS) major postapproval CMC changes in the production process, quality controls, equipment or facilities are summarized. It requires

the submission to the FDA and a subsequent review and approval by the agency prior to distribution of the drug product made using the change (see 21 CFR §§ 601.12 (b) (3) and 314.70 (g) (1)) [15, 21, 22.]. These changes have a **substantial** potential to impact product quality in a way that may affect the safety and/or effectiveness of the drug product [26]. Examples for CMC changes which require a PAS are the following:

- "Establishment of a new master cell bank or seed." [21, 22]
- "Changes in the source material or cell line." [21, 22]
- "Extension of culture growth time leading to a significant increase in number of cell doublings beyond validated parameters." [26]
- "New or revised purification process, including a change in column." [26]
- "A change in the chemistry or formulation of solutions used in processing." [26]
- "Changing the specification limits or modification(s) affecting the potency, sensitivity, specificity or purity determination of a method." [26]
- "Establishment of new analytical methods." [26]
- "Deleting of a specification or an analytical method." [26]
- "Scale up requiring a larger fermenter, bioreactor, and/or purification equipment (applies to production up to the final purified bulk)." [26]
- "Changes in the virus or adventitious agent removal or inactivation method(s)." [21, 22]
- "Extension of the expiration dating period and/or a change in storage temperature, container/closure composition, and other conditions, other than changes based on real time data in accordance with a stability protocol in the approved application." [26]
- "Changes in the qualitative or quantitative formulation or other specifications as provided in the approved application or in the regulations." [21, 22]

- "Changes which may affect the product sterility assurance, such as changes in product or component sterilization method(s) or an addition, deletion or substitution of steps in an aseptic processing operation." [21, 22]

- "Changes in the location (room, building etc.) of steps in the production process which could affect contamination or cross contamination precautions." [26]

Before all the changes listed in the sections above can be implemented in the manufacturing process of a commercial product, the manufacturer must demonstrate to the agency that there is no impact on the product quality. In some cases a re-validation of the process/analytical methods and/or lot release testing may be sufficient, but a thorough product comparability study (pre-change versus post-change product) could also be required.[4]

2.3.4 Comparability Exercise - Comparability Protocol

2.3.4.1 Comparability Exercise

As mentioned in section 2.2, if a CMC process change is required, it needs to be assessed based on "pre-change and post-change product" whether the intended post-approval CMC change will have an influence on the quality, safety and effectiveness of the product. Therefore, for evaluating manufacturing changes ICH guideline Q5E "Comparability of Biotechnological/Biological Products" should be taken into account [23]. According to ICH Q5E the aim of a "comparability exercise is to ensure the quality, safety and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes" [23]. Meaning, a "pre-change and post-change product" should be "highly similar" with respect to its quality attributes. As it is known that biopharmaceuticals are very sensitive even to slight changes in the manufacturing process [15] and due to all the specific features of biopharmaceuticals, also listed in section 1.2, it is not expected by the agency that the quality attributes of the "pre-change" and the "post-change" material is identical. Nevertheless, it has to be proven that both materials should be "highly similar" to make satisfactory justification of the safety and efficacy for a medicinal product. It has to be shown in an assessment that a specific set of structural features like protein folding, amino acid sequence and protein folding is

unaffected by process change. Slight modifications therein can affect their performance in humans and their immunogenicity [27]. This assessment can occur on a quality level but might be sometimes supported by comparability bridging studies depending on

- "The production step where the changes are introduced."[23]
- "The potential impact of the changes on the purity as well as on the physicochemical and biological properties of the product." [23]
- "The availability of suitable analytical techniques to detect product modifications." [23]
- "The relationship between quality attributes and safety and efficacy, based on overall nonclinical and clinical experience." [23]

Likewise, it is outlined in the guideline ICH Q5E that "for approved products an appropriate number of post-change batches should be analysed to demonstrate consistent performance of the process." [23] Further non-clinical and/or clinical studies on the basis of a batch to batch comparability would be required if a possible adverse effect on safety and efficacy has been identified in a comparability exercise [23, 28].

For conventional drugs, it is also elementary to compare the "pre-change" versus the "post-change" material. It is determined if the test results are "equivalent". Also in this case "equivalent" does not mean necessarily "identical". It is in fact more related to the maintenance of quality attributes like stability rather than a single performance of a test [24].

2.3.4.2 Comparability Protocol

In the U.S., it is possible to work within a comparability exercise by using a comparability protocol. The procedure of using a comparability protocol is in principle applicable for NDA and BLA submissions [25, 29]. According to FDA Guidance "Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information" a comparability protocol is defined as "[...] a comprehensive plan that describes the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes [...]" [25]. Comparability protocols of conventional drugs are

addressed in the separate FDA Guidance for Industry “Comparability - Protocols – Chemistry, Manufacturing, and Controls Information” [29].

Specific examples of manufacturing process changes that can be included in a comparability protocol for biopharmaceuticals are e.g.:

- Establishing a new working cell bank using a modified procedure [25]
- Adding, deleting or substituting raw materials (like buffer or media components) [25]
- Rearranging a production step [25].

A comparability protocol is pre-approved by the FDA with predefined acceptance criteria that will be used to confirm product comparability after introducing a change in the manufacturing process [43]. If a predefined acceptance criterion is not met the manufacturer can decide either not to implement the process change or to submit a PAS providing the justification why the process change does not adversely affect the safety and efficacy of the product [25].

In principle, a submission of a comparability protocol is not absolutely necessary for performing CMC changes but it helps the applicant to distribute the product sooner on the market than without using a comparability protocol. This is due to the fact, that a specified change can be classified in a lower reporting category if it is accompanied by an approved comparability protocol. This means e.g. if a PAS is submitted together with a comparability protocol the change can be categorised in the lower reporting category CBE (30) and if a CBE (30) is submitted with a comparability protocol it can be categorised as a CBE (0). The reason for this point is that by means of a comparability protocol the CMC change itself can be considered as well defined, e.g. by implementing analytical test methods, acceptance criteria or stability studies. This detailed and prospectively listed information helps the agency to obtain an overall picture if any potential adverse effect is caused by this change.

There are also CMC changes like facility changes for drug substance and/or drug product production where preapproval inspections become necessary to confirm if an acceptable cGMP compliance status is still given. In the comparability protocol it is then acknowledged that the product manufactured in different drug substance and/or

drug product manufacturing sites will not be distributed until the FDA confirmed a sufficient cGMP compliance status at the new manufacturing site [25].

In general a comparability protocol can be submitted in three different ways.

- Submitting a PAS:
  In this case the PAS only contains a comparability protocol. The aim is to obtain information on the reporting category of the change by the agency.

- Comparability protocol together with a PAS:
  Here, the comparability data are evaluated as part of the PAS. Product already manufactured with the change can only be distributed after approval of the supplement.

- Attachment of the comparability data to an original market application:
  This means that the comparability data are attached to an original market application obtaining the determined reporting category by the agency prior to generating product.

In all three cases, the comparability protocol must be approved prior to distributing the product. After a protocol is approved, the study results are submitted in a comparability report to the FDA. This comparability report is to contain the test results, deviations and corrective actions in comparison to the comparability protocol together with a summary and conclusions. [25].

In general, it is advisable for the applicant to discuss the comparability protocol and the postapproval change assessment with the FDA prior to execution to avoid any gaps in regulatory expectations, particularly in complex or not so obvious cases [15]

3. Pharmaceutical Development of Biopharmaceuticals

For developing conventional drugs as well as for biopharmaceuticals two approaches the so called “traditional approach” and the “Quality by Design (QbD) approach” are conceivable. The traditional approach is a more empirical and single variable approach, whereas the QbD approach is more scientific and risk-based from a regulatory point of view. It is a trend challenging of the conventional thinking in the pharmaceutical development. This flexible regulatory QbD approach is reflected in different ICH guidelines Q8, Q9, Q10 and Q11 (consultation) [30, 36, 47, 48] as well as in FDA guidances [38, 44,.] Hence, it becomes obvious that this approach is more and more claimed and requested by the regulatory agencies in the U.S, as well as in Europe. Hereinafter, both approaches “traditional” versus “QbD” are described and compared with each other showing a possible roadmap to deal with the new scientific and risk-based QbD approach.

3.1 Traditional approach to Pharmaceutical Development

The current status in the pharmaceutical development of biopharmaceuticals is the so called traditional or minimal approach. In the traditional approach, the pharmaceutical development is mainly empirical and the developmental research is often conducted with a single variable at a time. Multi variable interrelations that can affect the manufacturing process are not systematically taken into considerations [36]. Additionally, the manufacturing process is fixed with a focus on optimisation and reproducibility. In the traditional approach, the process validation is usually based on commercial scale batches [34, 36]. The legal basis for requiring process validation in the U.S. is 21 CFR § 211.110 (a). It is valid for drug product but may also be assigned for drug substance manufacturing. Here, it is defined that “control procedures shall be established to monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.” [31] Besides, in 21 CFR § 211.100 (a) the foundation for process validation is provided. There it is stated that “there shall be written procedures for strength, quality, and purity they purport or are represented to possess (...).” [32] According to ICH Q7 guideline, the approach for process validation is defined as the documented evidence that the process is able to operate within the established parameters. The process should perform effectively and reproducibly to

produce a product which meets its predetermined specifications and quality attributes [34]. The overall aim of process validation is to ensure batch uniformity and integrity. In general three approaches are possible: prospective, concurrent and retrospective validation with the prospective validation being the preferred approach [33]. In the traditional approach the guideline is to perform three consecutive production batches (consistency runs) at commercial scale [34, 36]. In the consistency runs of a process it is demonstrated that the process operated according to manufacturing procedures produces a product that meets release specifications [34, 36]. The results are presented in the filing in the corresponding Common Technical Dossier (CTD) sections.

In the traditional approach, the elements of manufacturing controls as e.g. in-process controls are fixed and are not supposed to be varied over time. For products developed according to the traditional approach the control strategy is usually derived empirically and relies on discrete sampling and end product testing [45]. The analysis is performed off-line. Product quality is monitored primarily by intermediates and end product testing. Possible variability in the process inputs like raw materials may result in a variability of the product quality [35]. This may cause variability in the produced product quality and lead to regulatory postapproval changes. Furthermore, in the traditional approach product lifecycle management is more categorised as reactive, i.e. problems are solved and corrective actions are taken if necessary [36]. This limits the traditional process validation approach as complex aspects which can influence the manufacturing process might not be considered early enough.

3.2 Quality by Design Approach to Pharmaceutical Development

In the mean time new regulatory concepts with respect to pharmaceutical development and process validation were developed. These are addressed in the QbD approach. However, the general regulatory requirements with respect to process validation stay in principle the same. The QbD approach is applicable for conventional drugs and biopharmaceuticals as well. According to guideline ICH Q8, QbD is defined 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” [36]. According to the new FDA Guidance for Industry “Process Validation: General Principles and Practices” “process validation is defined as the collection and evaluation of data from the process design stage through commercial production, which establishes scientific evidence

that a process is capable of consistently delivering quality product" [44]. In principle this means to take and use the knowledge gained during process development (e.g. during processing of material to supply clinical studies), to understand the sources of variation (e.g. raw materials like cell culture media or resins for purification) and the impact of such variation on the process and finally on the product quality (e.g. glycosylation and isoform pattern, aggregates formations or HCP/DNA level) and to accomplish a useful control strategy for ensuring that the process routinely delivers consistent product quality [35]. The sponsor or Marketing Authorisation Holder must show that different variables which can influence the process and the product quality are under control. Although the ICH Q8 guideline "Pharmaceutical Development" is focused on the CTD, module 3, section "P.2 Pharmaceutical Development", it is acknowledged that the principles and concepts that have been addressed in ICH Q8 are also applicable to the development and manufacture of the drug substance (see Final Concept Paper ICH Q11 "Development and Manufacture of Drug Substance" [37]). So all manufacturing aspects related to drug substance manufacturing can be deduced from drug product regulations, if applicable in the QbD approach. All data generated during laboratory, pilot and/or commercial scale studies are important information for consistently producing drug substance and drug product with an adequate product quality. Data obtained in pharmaceutical development or process validation will therefore demonstrate if the commercial scale is capable to produce acceptable product quality under commercial scale conditions [44]. The main goal of the QbD is "to develop a robust, well understood process, run within a design space of operating parameters and control strategy, thus meeting quality attributes" [52]. In this approach, changes in the manufacturing processes during development and lifecycle management are considered as helpful tools to gain more knowledge about the process performance. It also helps to define an acceptable design space which is described in more detail in section 3.3.3. The first step of generating a QbD approach was started in 2002 in the initiative "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach" and finally introduced into the FDA´s CMC review process in 2004, mostly for conventional drugs, with the aim of enhancing and modernising the regulation of the pharmaceutical manufacturing and product quality and to generate a scientific risk-based framework for making regulatory decisions easier for the pharmaceutical industry and the agency [35, 38]. In the meantime, the trend to QbD is getting more and more common for biopharmaceuticals, too. The major advantage of the

QbD approach is that it allows the applicant to continuously evaluate and update the process to ensure consistent product quality over time within the approved design space described in the dossier. It allows therefore a much higher flexibility in comparison to the traditional approach. Additionally, it facilitates more risk-based regulatory decisions within the BLA review and site inspections and a reduction of postapproval submissions as process changes within the design space will not require a review or approval by the agencies [46].

3.3 Roadmap for Implementation of an QbD Approach

In the following section an example of a roadmap for implementing a QbD approach is described with an overview illustrated in Figure 1.

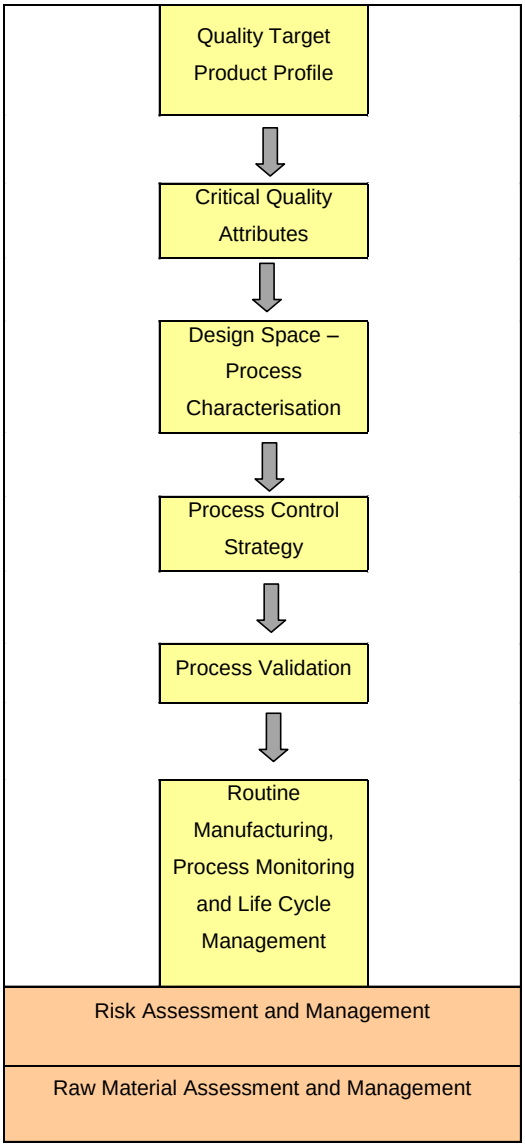

Figure 1: Roadmap for QbD implementation for biopharmaceuticals [35]

The general focus of the outlined QbD approach is based on a late stage process development, mainly drug product pharmaceutical development.

3.3.1 Quality Target Product Profile

The first step for the implementation of QbD is to define acceptable ranges for Critical Process Parameters (CPPs) and attributes to ensure acceptable performance of the product to meet the patient needs [35]. According to ICH Q8, a CPP is defined as “a

process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality" [36]. This will be identified in the Quality Target Product Profile (QTPP). The QTPP is defined as a "prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product" [36] according to guideline ICH Q8. This includes parameters like indication, dosage form and strength, route of administration, primary packaging system, therapeutic moiety release or delivery affecting pharmacokinetic characteristics like dissolution and the drug product quality criteria like sterility, purity and stability/shelf life appropriate for the intended marketed product [36]. In Table 1 a QTPP for a MOCK monoclonal antibody is depicted exemplarily. It was elaborated in the European Federation of Pharmaceutical Industries and Associations (EFPIA) working group "Goals and status of the Mock submission document on monoclonal antibody products by EFPIA" [39].

Table 1: Example of a QTPP for a MOCK monoclonal antibody [39]

Parameter	**QTPP Criteria**
Indication	Chronic disease (treatment of nervous breakdown)
Dosage Form	Lyophilisate for solution for injection
Dosage Strength	Nominal dose: 20 mg/vial
Route of administration	Subcutaneous (0.8 mL)
Reconstitution Time	≤ 2 minutes
Solution for Reconstitution	1 mL 0.9 % saline

Parameter	QTPP Criteria
Primary Packaging Material	2R glass vial, rubber stopper Material meets pharmacopoeial requirement for parenteral dosage forms
Shelf life	Two years at 2 – 8°C
Drug Product Quality Requirement	Meets pharmacopeial requirement for parenteral dosage forms as well as product specific requirements
Stability during administration	Reconstituted solution is stable for 24 hours at a temperature ≤ 30°C.

3.3.2 Critical Quality Attributes

After establishing the QTPP, the next step is to identify Critical Quality Attributes (CQAs). CQAs are defined 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” [36]. CQAs are used to set up appropriate specifications for the drug substance, drug product and the overall control strategy to ensure product quality. They are also used to design the molecule and the manufacturing process to meet patient needs and endpoints for safety and efficacy [49]. The first step to identify CQAs for biopharmaceuticals is achieving a full understanding of the molecular structure and product variants. CQAs may include product-related variants, process related impurities, formulation parameters and essential attributes like appearance (see Table 2). The identification of the CQA is performed by using risk assessment (see 3.3.7). In the following Table 2 QTPP criteria are translated into CQAs for a MOCK monoclonal antibody based on the examples listed in Table 1.

Table 2: Translation of QTPP criteria into CQAs for a MOCK monoclonal antibody [39]

QTPP criteria	**CQAs**
Nominal dose: 20 mg/vial	The quantity of drug substance has to reflect the expected nominal dose. The identity has to be the right one for patient safety.
Subcutaneous (0.8 mL)	Because of the injection route, isotonicity and pH are pharmacopoeial demands A parenteral injection has to be sterile for safety, and the desired volume of liquid has to be easily extracted in a syringe by the patient (extractable volume).
Meets pharmacopoeial requirement for parenteral dosage forms as well as product specific require-ments	Based on Ph. Eur. /USP: Content Uniformity, Extractable volume, Clarity, Particulate Matter, Sterility, Bacterial Endotoxins and Bioburden will be controlled.

As defined above the CQAs “should be within an appropriate limit, range or distribution to ensure the desired product quality” which is mirrored in the following table. The listed CQAs in Table 3 are based on the CQAs given in Table 2.

Table 3: An exemplary list of CQAs with their acceptable ranges for a MOCK monoclonal antibody [39]

CQAs	**Acceptable ranges**
Clarity (prior and after reconstitution)	≤ Reference suspension II
Content uniformity	0.95 - 1.05 mL
Identity	Conforms

CQAs	Acceptable ranges
Extractable volume	≥ 0.8 mL
Particulate Matter/Subvisible Particles	> 25 µm: ≤ 600 particles/vial > 10 µm: ≤ 6000 particles/vial
pH	5.8 - 6.2
Isotonicity	250 - 350 mOsm/kg
Quantity	22.5 - 27.5 mg/mL
Sterility	Sterile
Bacterial endotoxins	≤ 10 EU/mL

Further CQAs for drug substance and/or drug product may be identity (primary sequence), potency, posttranslational modifications (e.g. glycosylation, phosphorylation, glycation or methylation), product related impurities (e.g. deamidation, aggregation, oxidation, C-terminal lysine and misfolding) or process related impurities as HCPs and DNA and endotoxins [25].

3.3.3 Design Space – Process Characterisation

After setting up a risk assessment defining critical/non-critical or key/non-key process parameters and elaborating the CQAs of medicinal product the design space of the process needs to be characterised.

A detailed definition of a CPP is designated in section 3.3.1. Ranges for CPPs are established during process development, and changes to operating ranges will be managed within the quality system". [40] An example for a CPP could be a variation in column elution (e.g. buffer gradient) as it leads to higher aggregates which may increase immunogenicity [41]. According to the CMC Biotech Working Group, a Key Process Parameter (KPP) is defined as "an adjustable parameter (variable) of the process that, when maintained within a narrow range, ensures optimum process performance. A KPP does not meaningfully affect critical product quality attributes." [40] A KPP can be e.g. bioreactor temperature which is outside the range. This leads to lower productivity but will not have an influence on drug substance quality [41]. It is also possible that a CPP which was at first categorised as "critical" can be rated as a KPP, if it was shown that no impact on the product quality is given in a Proven Acceptable Range (PAR).

Besides, design space is classified as a "multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality" according to ICH guideline Q8 [36]. This means that the design space for a process step encompasses the acceptable ranges for CPPs of this step delivering a product of the desired quality [49]. The design space is in general developed by the applicant during late process development based on a thorough understanding of the process affecting factors and finally established during process characterisation in down scale or small scale models using multivariate mathematical tools like Design of Experiments (DoE) [49]. The design space is part of the BLA and will be subject to approval by the agencies. Working within the design space is not considered as a regulatory change [30]. However, exceeding of the design space is assessed as a regulatory change and mandates a postapproval change procedure [36]. In general, it can be differentiated between the Product Design Space and the Process Design Space [35] as outlined in the following.

Product Design Space

Once all CQAs have been identified, the concept of design space can be extended to product quality in the form of multidimensional design space, taking each CQA into consideration. The product design space which is the basis for setting up later prod-

uct specifications is dependent on different input data like stability, comparability and product characterisation studies, non-clinical and clinical data as well as the capability of the analytical methods [35]. The product design space is the basis for a process characterisation [35] which is described in more detail in the next section.

Process Characterisation - Process Design Space

After setting up an acceptable product design space, process characterisation can start to define the Proven Acceptable Ranges (PAR) of process parameters [42] and to select an appropriate manufacturing process. Process development and characterisation studies are mainly performed at laboratory scale to make them cheaper and faster. Therefore, developing a qualified or representative down scale model and designing studies using multivariate mathematical approaches like DoE are crucial to obtain meaningful results during process characterisation [35, 43]. As outlined in the Guidance for Industry "Process Validation: General Principles and Practices", process design is described as "defining the commercial manufacturing process based on knowledge gained through the development and scale-up activities" [44]. Furthermore, the aim of process design is defined "[…] to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes" [44]. Process design space means working within a PAR of a process. This results in producing a product which meets the relevant quality criteria [36]. However, a combination of PARs alone does not constitute the design space because PARs from univariate experimentation may lead to an incomplete understanding of interactions between the different process parameters or CQAs [45]. In Figure 2 the process design space is depicted in relation to the characterised and the operational ranges together with the Key and Critical Quality Attributes that may have an impact on the ranges. The Process Design Space includes the Normal Operating Range (NOR) with its setpoint and the PARs whereas the Process Characterisation Range exceeds the Process Design Space.

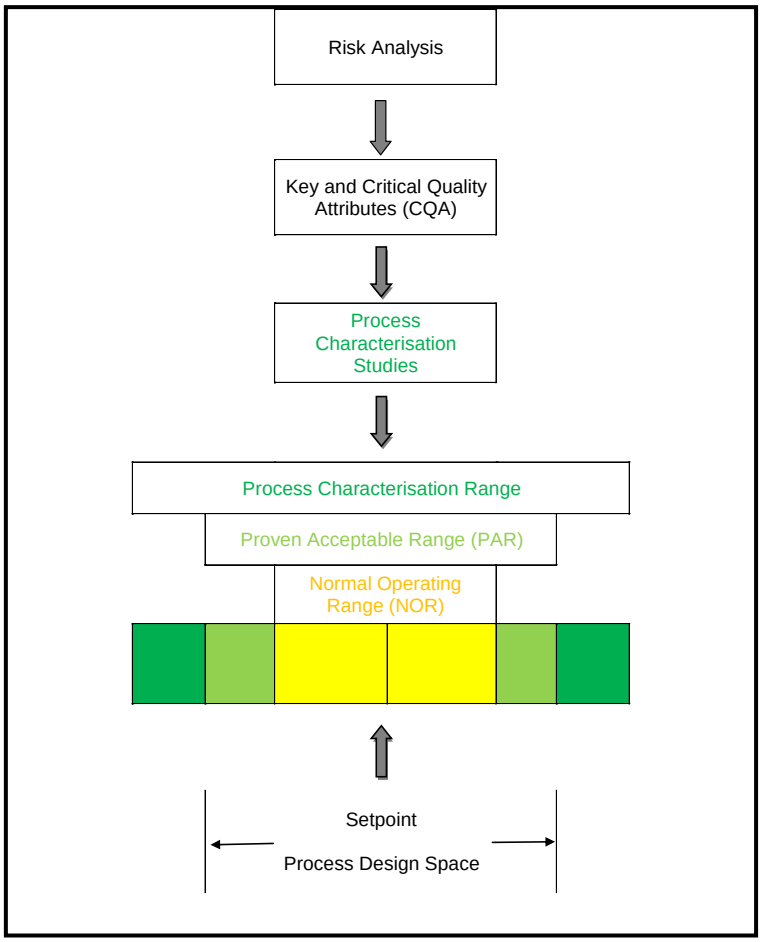

Figure 2: Process Design Space with NORs, PARs, characterised ranges and process setpoint influenced by Key and Critical Quality Attributes [46]

As outlined in Figure 2, process characterisation is performed in a three-tiered approach. First, a risk analysis (e.g. Failure Modes and Effects Analysis (FMEA)) is performed to identify critical process steps/CPPs to be addressed in process characterisation studies. For example in the filling process of vials critical process steps/parameters could be the filling speed and/or volume or correct stopper seating. The second step is to develop studies based on a DoE approach to study those CPPs and their interaction. In the risk analysis the effect of CPPs on the CQA like clarity (prior and after reconstitution), particulate matter/subvisible particles or sterility is assessed and evaluated. The third and last step is to define the process design space taking all these evaluations into account. In the example of the filling process of vials this could mean to set up a defined pump speed of 60 – 80 rpm and filling volume of 0.95 – 1.05 mL to avoid turbid solutions with too much subvisible particles and non sterile samples [39]. In the BLA, data of process characterisation and the de-

sign space for all key and critical operating parameters should be included (see section 3.5).

3.3.4 Process Control Strategy

Within a manufacturing process, CQAs like aggregates, HCPs or DNA need to be monitored continuously to ensure that the process runs are performed within the defined acceptable ranges [46]. According to ICH guideline Q10 a process control strategy is defined as a "planned set of controls derived from current product and process understanding that assures process performance and product quality" [47]. The process control strategy in the QbD approach is dynamic, meaning that the manufacturing controls can be changed or adapted within the design space depending on the particular CQA. In principle, the aim is to moderate the variability of process inputs like raw materials. Elements of a control strategy can be e.g. in-process testing, raw materials controls, specifications, product characterisation, stability studies, process validation testing, process monitoring and comparability studies. For aggregates several or all elements listed above are relevant to define a robust control strategy as the controlling of aggregates is very difficult. For CQAs like HCPs or DNA not as many controls are required in the process control strategy. The manufacturing process has sufficient process steps to remove process related impurities which was also proven during process validation [35]. Under the QbD approach, the process control strategy is derived using a systematic science and risk-based approach, i.e. testing, monitoring or controlling of CQAs is often performed earlier in the manufacturing process. Hence, the main focus is not only on the release testing. It is also conducted in-line, on-line or at-line [45] which is called Real Time Release (RTR). RTR is an important element of the process control strategy. Tests and monitoring of the manufacturing process can be performed as in-process testing rather than tests on the end product. However, RTR testing does not eliminate all end of product testing but it enables a reduced end product testing. Stability studies with its stability indicating methods are still required for all products according to the relevant guidelines [45]. A further helpful tool for establishing the right process control strategy is Process Analytical Technology (PAT). PAT is "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality" [38].

A major part of a process control strategy is still setting up the right specifications for drug substance and drug product based on the defined CQAs as they represent the ranges within which the product meets the desired product quality. Drug substance and drug product specifications are set up for biopharmaceuticals in accordance with ICH Q6B guideline [9] and are based on experiences on clinical and non-clinical studies [49].

3.3.5 Process Validation

In the traditional pharmaceutical development approach usually three consistency runs are performed at setpoint at commercial scale to demonstrate that the process will deliver an acceptable product quality [34, 36].

In the QbD approach, the objectives of process validation are in principle unchanged compared to the traditional approach. The main objectives of process validation remain that a process design yields a product meeting its quality criteria predefined in a process validation protocol. In the QbD approach generating risk assessments is unalterable. A risk assessment conducted prior to performing initial commercial validation batches can help to identify the areas where particular focus and data is needed to demonstrate the desired high level of assurance of commercial process robustness (see 3.3.7) [45.]. Besides, after setting up the design space, it has to be demonstrated during process validation that the process, operated within the design space, delivers an acceptable product quality. Therefore, the laboratory and pilot scales used to establish the design space should accurately mirror the performance of the commercial scale [35, 46]. In section 3.2, the FDA definition of process validation is described in detail. The approach for process validation is differentiated in a three-tiered approach [44]. Stage 1 is defined as “Process Design” meaning that the commercial manufacturing process is defined based on knowledge gained through development and scale up activities which can also be assessed as process characterisation (see section 3.3.3). In stage 2 “Process Qualification” the determined “Process Design” is evaluated for its suitability to reproducibly manufacture at commercial scale [44]. Here, it is not required to run the qualification batches at the outer limits of the design space at commercial scale as the design space must have been sufficiently explored during early developmental studies [45]. In the “Continued Process Verification” which is described as stage 3 in the FDA guidance ongoing assurances during routine production have to show that the process is under control. “Continuous Process Verifica-

tion" can be used as well in process validation protocols for the initial commercial production as for manufacturing process changes for the continual improvement throughout the product lifecycle [44].

3.3.6 Routine Manufacturing, Process Monitoring and Life Cycle Management

Process changes within the approved process design space will not require review or approval by the regulatory agencies [30, 46]. Therefore, it is possible to revise the operating range within the process design space without the need for postapproval submission. Exceeding the operating range can refer to unexpected process trend and will therefore cause an investigation. Working with the QbD approach is more flexible but does not mean to work out of control. Process and product consistency is still the main goal also for working with the QbD approach [46].

It is required to periodically evaluate the manufacturing process performance, the effectiveness of the control strategy and the suitability of the process design space which can be done in a Product Quality Review (PQR). Knowledge gained from a PQR, as well as from the manufacturing process for commercial supply, can be used to further improve process understanding and performance and to adjust the control strategy to ensure drug substance quality [30]. Additionally, it is also possible to update the design space. This may be the case when more knowledge and process understanding is gained with the first commercial batches under the approved BLA. However, this needs further process characterisation studies or re-validation of the process and requires an approval by the regulatory agencies prior to implementation [35, 46].

3.3.7 Risk Assessment and Management

According to ICH guideline Q9 a Quality Risk Management is defined as "a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle" [48]. A typical risk management process consists of a:

- Risk assessment
- Risk control
- Risk review. [48]

The objective of setting up a risk assessment is to determine which quality attributes may have a potential to affect the safety and efficacy of the product [49]. A risk is considered as low if relevant clinical data are available and demonstrates that no adverse effects on safety or efficacy are detectable as e.g. the formation of aggregates or potential oxidised species. In contrast, a risk is classified as high if clinical data indicate that an adverse impact on safety or efficacy is given [25]. Risk assessments support a risk decision to be made within a risk management process. Within a risk assessment critical/non-critical or key/non-key process parameters can be identified.

Tools of a risk management could be e.g. FMEA, Fault Tree Analysis or Hazard Analysis and Critical Control Points. Risk assessments can be performed e.g. to assess the CQAs, manufacturing process and analytical method capability, stability, criticality of raw materials (see section 3.3.8), process and product comparability. Within a product lifecycle it may be necessary to revise and review the risk assessments when for example new data from clinical or non-clinical studies are available [35,.48].

Risk assessments are submitted in the BLA where they are the basis to justify the proposed flexible regulatory approach [50].

Risk assessments in which risks have been identified, analysed and evaluated are the basis for setting up a sound risk control strategy to either reduce, eliminate or to accept a risk [35, 48]. The relevant points which may be addressed for controlling of risks are:

- “Is the risk above an acceptable level?” [48]
- “What can be done to reduce or eliminate risks?” [48]
- “What is the appropriate balance among benefits, risks and resources?” [48]
- “Are new risks introduced as a result of the identified risks being controlled?” [48]

According to ICH Q11 guideline (DRAFT), the goal of a risk assessment is to convey “an understanding of the purpose of the study, the data collected, how it was analysed, the conclusions reached, and the impact of the study on the manufacturing process or further development of the manufacturing process” [30]. Furthermore, “the particular parameters and ranges studied should be described and discussed in rela-

tion to the proposed conditions for the commercial manufacturing process." [30] In a risk assessment "tools and study results on which the design space is based" should be adequately addressed [30].

As a risk management should be performed continuously, a review or monitoring mechanism should be integrated. The results of a risk management process should be reconsidered with respect to new knowledge and experience and decided risk acceptance criteria in the risk control strategy. The frequency of a review is based on the risk level [48]. In general, risk based approaches can be used in defining complex issues like immunogenicity, critical quality attributes, process risk assessments (see section 3.3.3) and raw material criticality risk assessment [35] (see section 3.3.8).

3.3.8 Raw Material Assessment and Management

Especially for biopharmaceuticals a reasonable raw material management is required because in the manufacturing process many not well-defined raw materials with a certain lot-to-lot variability like hydrolysates in cell culture media or chromatographic resins are used. In a raw material assessment it needs to be differentiated in critical, key or non-key raw materials [35].

Critical raw materials have a significant impact on the product quality. Here, an extensive characterisation is required. For these raw materials acceptance criteria need to be developed. Meeting these acceptance criteria means that the process is still under control. Within the ranges defined by the acceptance criteria these critical raw materials leads to an acceptable product quality [35].

Key materials do not have a significant impact on the product quality but they can influence the product consistency. Therefore, they also need to be well-characterised, not for each raw material lot but possibly in a bracketing concept [35].

Non-key materials are the remaining raw materials which are the majority. They are handled as in the traditional pharmaceutical manufacturing with the internal quality system of the manufacturer [35].

3.4 Handling of Postapproval CMC Changes in a QbD Approach

Implementing the QbD approach, the CMC Postapproval Management Plan (PMP) has been suggested in the U.S.. It includes commitments, reporting requirements and supporting data required for future changes based on risk assessments and sci-

entific knowledge presented in a marketing application [51, 52]. Hence, it needs to be submitted and approved by the FDA [52]. According to the FDA, the "CMC PMP provides a risk-based scientific basis for applicants to manage post-approval changes, which could lead to significant reduction of CMC supplements" [51]. So far, it is written on a voluntary basis and could be part of the CTD in section 3.2.R.3 or module 1. The CMC PMP serves as a communication tool between the applicant and the FDA. It can be applied both for drug product and drug substance. It differentiates changes like CPPs that should be reviewed by regulatory agencies from those changes like operational parameters that are managed by the manufacturer's internal quality systems [51]. A CMC PMP considers typical changes which can occur during the lifecycle of a product. Knowledge of the process and product and the lifecycle regulatory commitments are taken into consideration in a PMP. It should contain reporting requirements that permit innovation and improvements to be implemented in the manufacturing process. Besides, it should serve as a tool to assure regulatory reporting to the agencies. "With the inclusion of increased data that supports items such as CQAs, process parameters, and the design space, it will be imperative to clearly delineate between information that is provided for review and approval of the initial application and commitments that will continue throughout the lifecyle of a product. " [52] The PMP commitment section in a BLA would contain a summary of the overall control strategy commitments for e.g. raw material controls, CPPs, excipient control and primary packaging [52].

In the U.S., widening a PAR for a CPP requires a manufacturer to submit a PAS to the FDA. In the PMP the applicant could e.g. propose the testing and acceptance criteria, based on product knowledge, by which they would demonstrate that the widened range does not negatively affect the product quality. The applicant could then request that this future change, when needed, be submitted as a CBE (30) [51].

In summary, the aim of the proposed PMP is to simplify planning for approval timelines and to significantly reduce the costs for change implementation in manufacturing [51].

3.5 Roadmap for Documentation of a QbD Approach in Regulatory Dossiers

As mentioned in section 3.4, the PMP may be implemented either in module 1 or in section 3.2.R.3 of the CTD [43].

In the Quality Overall Summary (QOS) of module 2, cross-reference data that describes the design space and control strategies can be implemented [43].

In module 3 of the CTD, the product design space is documented in form of in-process, drug substance or drug product specifications in CTD sections S.2.4/P.3.4 “Controls of Critical Steps and Intermediates” and S.4/P.5 “Control of Drug Substance/Drug Product” defining and justifying acceptable ranges [36, 39, 43]. In sections S.2.2/P.3.3 “Description of the Manufacturing Process and Process Controls”, S.2.3 “Control of Materials”, S.6/P.7 “Container Closure System” and P.4. “Control of Excipients”, further elements related to the process control strategy can be included [30, 36]. The process design space is described in the filing as an element of the proposed manufacturing process. It can be implemented for drug substance and drug product in the CTD sections S.2.2/P.3.3 “Description of Manufacturing Process and Process Controls”. In sections S.2.6 “Manufacturing Process Development” and P.2 “Pharmaceutical Development” (P.2.1 “Components of the Drug Product”, P.2.2 “Drug Product” and P.2.3 “Manufacturing Process Development”) the process development is summarised which is the basis for the Process Design Space [36, 39, 43]. Quality risk assessments which are used to guide and justify development decisions like risk analyses can be summarized in section S.2.6 [30]. Information regarding process validation is implemented, like in the traditional approach, in section S.2.5/P.3.5 “Process Validation and/or Evaluation” [39].

Sections that do not contain QbD information and contain only information that would be included in a traditional application should be identified with the term "traditional content" [43].

4. Discussion and Outlook

As outlined in section 3.1, the traditional approach does not focus on different variations of variables in the manufacturing process. The main aim is rather to show that the process is able to consistently produce material in consecutive runs without broadly evaluating potential effects of material variations or variations in the manufacturing process itself. This is shown during process validation at commercial scale. It is a one-dimensional approach and does not take multivariate parameters into consideration. Therefore, in the traditional approach the postapproval CMC changes require more regulatory agency endorsement compared to the QbD approach. In the traditional approach it has to be demonstrated individually e.g. in a comparability protocol whether the “post-change product quality” will be still comparable to “pre-change product quality”. The QbD approach is in contrast a more risk-based approach taking multivariate parameters of the process into consideration. It is a systematic approach which is based on scientific experiences where data are gained from the whole pharmaceutical development until scale-up activities. The aim of QbD is to act rather preventive than reactive. In the following Table 4 the main aspects of the traditional approach versus the QbD approach are listed and compared according to ICH guideline Q8.

Table 4: Comparison of the traditional approach versus QbD approach to the pharmaceutical development based on ICH guideline Q8 [36]

Aspect	Traditional Approaches	QbD Approaches
Overall Pharmaceutical Development	Mainly empirical	Systematic, relating mechanistic understanding of material attributes and process parameters to drug substance/drug product CQAs
	Developmental research often conducted one variable at a time	Multivariate experiments to understand product and process Establishment of design space PAT tools utilised

Aspect	Traditional Approaches	QbD Approaches
Manufacturing Process	Fixed Validation primarily based on initial full-scale batches Focus on optimisation and reproducibility	Adjustable within design space Lifecycle approach to validation and, ideally, continuous process verification Focus on control strategy and robustness Use of statistical process control methods
Process Controls	In-process tests primarily for go/no go decisions Off-line analysis	PAT tools utilised with appropriate feed forward and feedback controls Process operations are tracked and trended to support continual improvement efforts post-approval
Product Specifications	Primary means of control Based on batch data available at time of registration	Part of the overall quality control strategy Based on desired product performance with relevant supportive data
Control Strategy (compare also Product Specifications and Process Controls in Table 4)	Drug substance/drug product quality controlled primarily by intermediates (in-process materials) and end product testing	Drug substance/drug product quality ensured by risk-based control strategy for well understood product and process Quality controls shifted earlier into the process, with the possibility of real-time release testing or reduced end-product testing
Lifecycle Management	Reactive (i.e., problem solving and corrective action)	Preventive action Continual improvement is facilitated

Evaluating Table 4, it becomes obvious that the QbD approach in the pharmaceutical development is much more complex compared to the traditional approach. Using the QbD approach is not the easiest way of developing and evaluating a manufacturing process. The goal of the QbD approach is to improve and ensure patient´s needs regarding safety and efficacy of a drug product on a risk-based approach from the start of pharmaceutical development. A clear benefit of working with the QbD approach is that it allows the process to be continually evaluated. Furthermore, it facilitates continuous improvements and innovations to ensure product quality over time, acknowledges the extensive understanding of the manufacturing process and product gained through the development of the design space or through manufacturing experience. Furthermore, it reduces non-value added work. The demonstration of extensive process knowledge in the dossier for marketing application, combined with established robust and effective quality systems to monitor manufacturing process performance, provides health agencies assurance. This finally allows them to reduce regulatory burden of postapproval change supplements while still meeting legal and regulatory expectations [52].

This new QbD approach of handling postapproval CMC changes (in Europe as well as in the U.S) will be on the one hand a great chance for the pharmaceutical industry as it eases dealing with manufacturing changes. On the other hand it challenges the pharmaceutical industry to set up a rather extensive program during product development at early clinical stages towards BLA always balancing the risks, costs and benefits of a product. In this context, it needs to be considered that from 10.000 molecules evaluated in pharmaceutical development during preclinical testing five medicinal products reach clinical phase I. Thereof, two to three medicinal products reach clinical phase II and thereof one to two medicinal products clinical phase III. At the end, from 10.000 molecules tested in pre-clinical studies one drug accomplishes approval for going into the market within an estimated development timeframe of 10 or more years [53]. This shows on the one hand the dimension of costs for pharmaceutical development for a medicinal product and on the other hand the low success rate of a medicinal product to become a market product. Applying the QbD approach in addition, leads to much higher costs and efforts right from the start of pharmaceutical development. In consequence, implementing the QbD approach may be a real challenge for companies, especially for Small-Medium-Enterprises. The high costs during

product development could promote e.g. a licensing or selling of a product at early clinical stages.

In the meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharamcology (ACPS-CP) industry representatives identified further challenges of the QbD beside the significantly increasing drug development costs. They feared that the QbD approach slows down pharmaceutical development and approval times [54]. In general, it was addressed in this meeting that the applicants are not aware of what the FDA expects. For applicants it is e.g. not clear what should be part in a QbD application, what are required or supportive information in a QbD application and what does quality system in general mean. Therefore, it was suggested that the FDA should publish a QbD status report with examples and lessons from companies that have implemented QbD priniciples and technologies successfully. Another suggestion was to establish a QbD resource center for facilitating QbD tools for identifying any potential gaps in the implementation of QbD. This center could serve as an information platform between pharmaceutical industry and agency showing and outlining the clear benefits of the QbD approach [54]. The outcome of this ACPS-CP meeting demonstrates that dealing with the QbD approach is still not fully understood and that further clarification from the agency is necessary.

So even if it seems at first glance that costs and efforts in pharmaceutical development using QbD are much higher, the clear benefits of the QbD approach are to reduce material rejections and batch failures in manufacturing. As a consequence, also reprocessing and recall procedures as well as the submission of variations are reduced [52]. Hence, the higher costs and efforts at the beginning of the pharmaceutical development may be levelled or returned into profit when the product is placed on the market.

So far, the minimal or traditional approach is still accepted for an application but the QbD approach is more and more encouraged by the agencies. This trend is supported by the FDA´s Manual of Policies and Procedures (MAPP) 5016.16 recently issued [50], in which it is pointed out that the reviewers at FDA have to ensure that applications contain at a minimum information on pharmaceutical development described by ICH Q8 and “whether an application includes sufficient enhanced knowledge that demonstrates the applicant´s understanding of material attributes, manu-

facturing processes and controls for product quality to support the proposed flexible regulatory approach" [50]. As the focus of the agencies will be reinforced on the QbD approach, the sponsor or marketing authorisation holder will come more and more under pressure to justify a deviation from this new approach. In a recent press release, the FDA and European Medicines Agency (EMA) started a three years pilot program with respect to evaluation of QbD applications [55]. In this program, QbD data of the dossier can be submitted in parallel to both agencies. The data will still be evaluated separately at both agencies but with a regular exchange of their views with respect to issues like pharmaceutical development, design space and RTR testing. At the end, the goal is to generate a joint list of questions which is then forwarded to the applicant. Participation in this program is voluntary and for the time being it is envisaged for conventional drugs or small molecules only. At EMA the focus of this pilot program will be on new MAA, quality related scientific advice requests and type II variations. At FDA mainly NDA, PAS and CMC meeting requests are handled. This pilot program gives the clear hint that the agencies support working with the QbD approach, preliminarily for small molecules, but for the future also more and more for biopharmaceuticals [55].

As previously stated, the QbD approach is applicable for both biopharmaceuticals and small molecules. It is obvious that establishing the QbD approach for biopharmaceuticals is more sophisticated due to the usage of cell based systems and a complex manufacturing and purification process. Furthermore, it has to be noted that the QbD approach for biopharmaceuticals is at present at the beginning, meaning that the QbD approaches are so far only emerging in different suggestions of MOCK approaches like for monoclonal antibodies [39, 40]. Furthermore, these suggestions still have to be translated, adapted and elaborated for the applicant´s own specific product and/or process. Currently, the practices with respect to pharmaceutical development of biopharmaceuticals can not be assessed as "black or white" but vary and lie somewhere between the two pure approaches depicted in Table 4 [36].

Summarising, the handling of postapproval CMC changes is increasingly influenced by more regulatory change control flexibility and expanded change protocols. The integration of QbD according to ICH Q8, Q9 and Q10 introduces a clear change in the regulatory landscape as postapproval CMC changes will be more and more

driven by an increased reliance on quality systems change control, risk-based evaluation and reduced requirements for prior regulatory agency approval [52].

5. Summary

A variety of medical illnesses can presently only be treated by using biopharmaceuticals. Biopharmaceuticals thus constitute an extremely important class of pharmaceutical products, whose manufacturing is a complex field with respect to producing a safe and effective medicinal product.

Due to the very specific features of biopharmaceuticals the regulation of biopharmaceuticals differs in comparison to conventional drugs. The FDA, responsible for regulating drugs (both biopharmaceuticals and conventional drugs), in the U.S. approves biopharmaceuticals for marketing through the BLA and conventional drugs through the NDA process. The BLA and NDA is a request for permission to introduce a medicinal product into interstate commerce.

When a product is first approved, its manufacturing process represents the current technology standard for manufacturing and follows the cGMPs standard for regulatory compliance. After approval, market demand, technological advances, changed GMP standards, raw materials sourcing or manufacturing experience may require that the approved process needs to be modified [52]. Therefore, process changes are an expected aspect of pharmaceutical manufacturing. However, it is known that biopharmaceuticals are very sensitive even to slight changes in the manufacturing process [15] and due to all features of biopharmaceuticals, it is not expected that the quality attributes of the “pre-change” and the “post-change” material is identical. Nevertheless, it has to be proven that both materials should be “highly similar” to make satisfactory justification of the safety and efficacy of a medicinal product. This needs to be addressed in a comparability exercise. The assessment can occur on a quality level but might be sometimes supported by comparability bridging studies [23]. After evaluating whether the changes of the manufacturing process have a minor, moderate or a substantial effect on the quality, safety and efficacy of a product by the applicant the FDA needs to be notified. Reporting to FDA is performed by an Annual Report for minor changes, by a CBE (0 or 30) for moderate changes and a PAS for major changes. Especially for biopharmaceutical products, due to their complexity, the quality of a “pre-change” versus “post-change” product and thus its impact on safety and efficacy needs to be assessed. Therefore, it advisable or even mandatory to run a comparability exercise by using a comparability protocol.

In the pharmaceutical development, for conventional drugs as well as for biopharmaceuticals, the “traditional approach” and the “QbD approach” are conceivable. Currently, a clear trend towards QbD can be observed. The traditional approach is a more empirical and single variable approach, whereas the QbD approach is more scientific and risk-based from a regulatory point of view. The flexible regulatory QbD approach is a trend that challenges the conventional thinking in pharmaceutical development. It is already reflected in different ICH guidelines Q8, Q9, Q10 and Q11 (consultation) [30, 36, 47, 48] as well as in FDA guidances [38, 44] meaning that this approach is more and more claimed and requested by the regulatory agencies in the U.S. as well as in Europe. It is expected that introduction of a QbD approach in development will have tremendous impact on the handling of CMC changes in the maintenance phase of a product, both in terms of frequency and complexity of such changes.

It becomes obvious that establishing the QbD approach for biopharmaceuticals is sophisticated due to the usage of cell based systems and a complex manufacturing and purification process. However, this new QbD approach of handling postapproval CMC changes by the agencies may be on the one hand a clear benefit for the pharmaceutical industry as it eases dealing with manufacturing changes. On the other hand it challenges the pharmaceutical industry in setting up a quite complex program for pharmaceutical development already at early clinical stages.

Handling postapproval CMC changes in a QbD setting is characterized by more regulatory change control flexibility and expanded change protocols. Furthermore, it allows the applicant a continuous evaluation and update of the process to ensure consistent product quality over time within the approved design space described in the dossier and facilitates a reduction of postapproval submissions as process changes within the design space will not require a review or approval by the agencies [46].

Introduction of QbD constitutes a considerable change in the regulatory landscape as postapproval CMC changes will be driven by an increased reliance on quality systems change control, risk-based evaluation and reduced requirements for prior regulatory agency approval [52]. Consequently, despite the complexity of the approach and the necessity of higher investments at early stages of pharmaceutical development, the QbD approach can be a great chance for the pharmaceutical industry.

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