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Chapter 6

QbD Implementation in Biotechnological Product Development Studies

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Additional information is available at the end of the chapter

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Abstract

Biotechnological drug development is an extensive area still growing and coming into prominence day by day. Since biotechnological product manufacturing is irreversible, highly expensive, and contains so many critical parameters throughout the process, quality control tests applied to the finished product become inefficacious; therefore, maintaining predefined quality is crucial. Quality by Design (QbD), a systematic approach, is designing and optimizing of formulation and production processes in order to provide a predefined product quality by following a risk and scientific-based path. Determining the critical variables for biotechnological products and their manufacturing via risk assessment is the first and most vital stage of QbD approach, before exploring the multivariate relations among the independent and dependent critical variables by mathematical modeling with the assistive technologies. Response Surface Method (RSM), Artificial Neural Network (ANN), and Genetic Algorithm (GA) are some of the assistive technologies used to perform mathematical modeling. After modeling, additional knowledge is vested and this provides the chance to find a range in which the product quality is always ensured, called as "Design space". So, product quality is procured all along the process by keeping the critical variables under control with less effort, money, and mistakes.

Keywords: biotechnology, production, QbD, ICH

1. Introduction

Pharmaceutical manufacturing is a complicated process from formulation to the final product. It is crucial to understand that multivariate interactions between raw materials and process

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conditions take place in the manufacturing process to ensure processability and product quality. Despite continuous innovations in the pharmaceutical industry for developing new, futuristic drug products, there have been a repeated set back due to low quality and manufacturing standards. The studies and tests required to deliver a new drug to end-users takes up to 15 years, and cost over 800 million $. Even after a drug is invented, due to the proven incapability for its safe manufacture in a large scale and incompliance with the relevant specifications, its development may fail. The approval process duration and the requirement to start over a development cycle because of any changes resulted from stalemates have both given rise to concerns for decades. Nowadays it is known that this process, involving a significant amount of paperwork for evaluation and approval of new product submissions, is slow and overwhelming and causes excessive delays [1].

2. ICH Guidelines: objectives and history

Traditional pharmaceutical manufacturing is accomplished by using batch processing with quality control testing conducted on samples of the finished product. Despite the loss of too many products and investment, this conventional approach has been considered sufficient in providing quality pharmaceuticals to the public for many years. However, innovation in product and process development, process analysis, and process control can provide significant opportunities for improving pharmaceutical development, manufacturing, and quality assurance [2].

Process change is an expected aspect of pharmaceutical manufacturing. To keep pace with advancing technologies and improvements in the manufacturing process, many process changes are made resulting from increased process knowledge. When a product is first approved, its manufacturing process represents the current technology standard for manufacturing and follows the current standards for regulatory compliance. After approval, the approved process may need to be modified due to changes in market demand, technological advances, manufacturing standards, raw materials sourcing, or manufacturing experience. Traditionally, postapproval changes require regulatory agency approval before implementation. The increasing number of new products in addition to the number of marketed products seeking postapproval changes has placed a significant burden on the government and industry to submit and review data to comply with existing requirements. Thus, we need to identify a path forward that will enhance substantial product and process knowledge using risk assessment tools and quality systems to ensure product safety and efficacy [3].

Because of all these reasons, the drug industry experienced major developments in production information, quality management systems, and risk management in recent years. The industry developed modern production tools that can assist in ensuring product quality [1]. Thus, Food and Drug Administration (FDA) introduced the amendments in the current Good Manufacturing Practices (cGMP) to the pharmaceutical industry, to improve and modernize the rules that regulate the pharmaceutical product manufacturing and product quality since 2002, in accordance with the developments in the twenty-first century. International Conference on

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Harmonization (ICH) is a forum for registered institutions and experts from the pharmaceutical industries in the United States (US), Japan, and European Union to harmonize the technical requirements for pharmaceutical products in three regions. It provides up-to-date guidelines bringing a new approach called Quality by Design (QbD) to the pharmaceutical industry [4]. The new series of quality guidelines (Q8, Q9, Q10, and Q11) were published by ICH regarding the QbD concept which was introduced into the FDA's chemistry, manufacturing, and controls (CMC) review process in 2004 [5]. Subsequently, in 2005, the guideline Q8 "pharmaceutical development" of the International Conference on Harmonization (ICH), which focused on the content of the module 3.2.P.2 of the common technical document (CTD), was published to present a roadmap for a proper QbD implementation [1]. These improvements have added new dimensions to the pharmaceutical industry [6].

The concept of "Quality by Design" has been identified as an approach which has something to do with a developed scientific comprehension of crucial process and product qualities by designing controls and tests on the basis of the scientific limits of comprehension which is determined during the progress, and using the knowledge acquired during the life cycle of the product to improve an amelioration environment permanently in this framework [2].

2.1. ICH Q8

The Q8 guideline is intended to provide guidance on the contents of section 3.2.P.2 (pharmaceutical development) for drug products as defined in module 3 of the common technical document (ICH guideline M4). The pharmaceutical development section aims to provide a comprehensive understanding gained through the application of scientific approaches and quality risk management on the product and the manufacturing process for reviewers and inspectors. The guideline also indicates areas where the greater understanding of pharmaceutical and manufacturing sciences leads to flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided. It is first produced for the original marketing application and can be updated to support new knowledge gained over the lifecycle of a product [7].

2.2. ICH Q9

QbD is a systematic approach to pharmaceutical development for designing and developing formulations and manufacturing processes that can generate a prescribed product quality. In other words, QbD claims that "quality cannot be tested into products; it should be built-in during the designing phase". Based on this, the ICH guidelines Q9, "quality risk management," and Q10, "pharmaceutical quality system," were published. The guideline Q9 offers principles for quality risk management that can be applied to different aspects of drug quality [1]. The purpose of this document is to offer a systematic approach to quality risk management [8].

Quality risk management tools can be used in various stages of pharmaceutical operations, such as development, production, laboratory controls, packaging, and labeling, and also in inspection and assessment activities. The quality risk management guideline contains two main principles of the risk management model. These principles explain the risk management

process and the terminology and tools used for risk evaluation. The aim of the risk management guideline is to create a common understanding to realize risk management, including risks that cover products, processes, and facilities, and risks that affect robustness of the quality system are evaluated, and controls related to risk mitigation are also performed [6].

Consequently, the Q9 explains what risk is, how it is evaluated, and where quality risk management could be applied. It specifically provides guidance on the principles and some quality-risk management tools that can allow making more effective and consistent risk-based decisions by regulators and industry, regarding the quality of drug substances and drug products across the product lifecycle [8].

2.3. ICH Q10

ICH Q10 identifies one multi-purpose model for an effective pharmaceutical quality system which is based on International Standards Organization (ISO) quality concepts and it contains applicable GMP regulations and complements ICH Q8 and ICH Q9. ICH Q10 is a pharmaceutical quality system model that can be implemented throughout different stages of life cycle of a product. Therefore, whether the content of ICH Q10 is additional to the current regional GMP requirements or not is optional. ICH Q10 demonstrates industry and regulatory authorities' support for an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world for public health. Applications of Q10 guideline enables innovation and incessant improvement and empowers the link of pharmaceutical progress. ICH Q10 should be practiced in a way that is appropriate to each product's lifecycle phase [1, 9].

2.4. ICH Q11

ICH Q11, "development and manufacture of the drug substances," was published by ICH in 2012. Q11 was created for drug substances, including biotechnological and biological entities, and is related to drug substance manufacturing and development. Various pharmaceutical development and drug substance understanding approaches are described, and Q11 serves as a guideline on the type of information that should be provided in module 3 CTD sections 3.2.S. 2.2–3.2.S.2.6 [1, 6].

2.5. ICH Q12

ICH Q12, "technical and regulatory considerations for pharmaceutical product life cycle management," is intended to work in compliance with ICH Q8–ICH Q11 guidelines and will give an opportunity to the management of postapproval changes in a more predictable and efficient way throughout the life cycle of the product. After complete pursuance of this guideline, upgraded innovation and continual improvement, and more robust quality assurance and reliable supply of product will be expected. It will allow regulators to better understand, and have more confidence in a firm's pharmaceutical quality system (PQS) for management of post-approval changes [10].

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3. QbD road map

QbD is a systematic product development approach that begins with predefined objectives and emphasizes understanding of the product and process based on firm science and quality risk management, as defined in ICH Q8 guideline. Quality risk management and knowledge management are the two basic components of QbD [4].

QbD is a methodical, erudite, risk-oriented, holistic, and proactive approach to pharmaceutical progress that begins with predefined objectives, and underlines product and process comprehension and process control. QbD requires that quality-improving erudite methods might be used upstream in the research, progress, and design phases to ensure that quality is designed into the product process at the earliest possible phase [2].

A vital component of QbD is comprehension of the needs of the patient and the certain quality arrogates of the product concerned to security and impressiveness. Thereby, to apply QbD, it is crucial to have a principal comprehension of the functional relationships among patient necessities, product quality arrogates, analytical abilities, and the production process. QbD works inside the design space (DS) obtained by considering critical formulation and process parameters and so there is no need for product quality verification through final quality test. This knowledge is gained during development and grows with more manufacturing experience through process characterization, scale up, technology transfer, manufacture, and increased patient exposure to the product. This approach makes it feasible to use data gathered from development works performed to create a design space for achieving continuous development. By this way, it is possible to ensure changes in the trade with the change control method, without the need for confirmation from the authority. Regarding the life cycle of the product, the most up-to-date pharmaceutical and engineering information is used [4, 5].

A complete QbD study should include the following four key elements: (i) define a target product quality profile (goals) based on prior scientific knowledge; (ii) design product and manufacturing processes that satisfy predefined goals; (iii) identify potentially high risk attributes and/or parameters and sources of variability by using risk assessment and scientific knowledge to obtain the design space with controlled experimental studies; and (iv) develop a control strategy to control manufacturing processes to produce consistent product quality over time by operating within the established design space, thus assuring that quality is built into the product during the manufacturing, storage, and distribution of the product [2, 11].

Implementation of QbD-based strategies in pharmaceutical development would provide excellence and significant time shortening in product development, and enormous flexibility in regulatory compliance. It has been emphasized before if the principles described in the ICH Q8, Q9, and Q10 guidelines are implemented together in a holistic manner, this will ensure further that the patient will receive product that meets the critical quality attributes (CQAs) [1].

3.1. Determination of quality targets

In order to design quality into a product, the requirements for the product design and performance must be well understood in the early design phase [12]. By beginning with the

end in mind, the result of development is a robust formulation and manufacturing process with an acceptable control strategy that ensures the performance of the drug product [11].

Target product profile (TPP) describes the general objective of the pharmaceutical product development program and provides information about the development works. ICH Q8 needs specifying of properties crucial for the quality of the prepared pharmaceutical product, in regard to intended use and route of administration and valuation of intended use of the product and route of administration is performed with the TPP [4]. Pharmaceutical companies will use the desired labeling information to establish a target product profile that describes anticipated indications, contraindications, dosage form, dose, frequency, pharmacokinetics, route of administration, maximum and minimum doses, presentation of pharmaceutical product, and target patient population [12].

The quality target product profile (QTPP) is derived from the desired labeling information for a new product and 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" [11, 12]. In addition to defining the design requirements of the product, the QTPP will help identify critical quality attributes such as potency, purity, bioavailability or pharmacokinetic profile, shelf life, and sensory properties [12].

A critical quality attribute is a physical, chemical, biological, or microbiological feature or property that should be within a proper limit, range, or distribution to provide the required product quality [11].

The concept of criticality can be used to explain any feature, importance, or characteristics of an active substance, component, raw material, finished product, or device; or any process characteristics, parameters, conditions, or factors in the finished product [4].

3.2. Determination of critical parameters

A material attribute or process parameter is critical when a realistic change in that attribute or parameter can significantly impact the quality of the output material [11].

The parameter expresses a measurable or countable characteristic of a system or process. Parameters are usually considered as features related to manufacture, such as temperature and mix speed, or as characteristics of equipment or process. Features are considered as characteristics of materials (such as melting point, viscosity, and sterility). However, it must be noted that there are no absolute borders between features and parameters [4].

"Quality attribute hazardousness is initially depended on burden of harm and does not change as a result of exposure management. Process parameter hazardousness is attached to the parameter's effect on any crucial quality arrogates. It is depended on the probability of occurrence and discoverability, so it can change as a result of exposure management" [13].

3.3. Quality risk management

Risk management principles are effectively utilized in many areas of business and government. The importance of quality systems has been affirmed in the pharmaceutical industry too, and

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it is becoming apparent that quality exposure management is a precious compound of a sufficient quality system.

Commonly, risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. Regarding pharmaceuticals, although there are various stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality has prime importance.

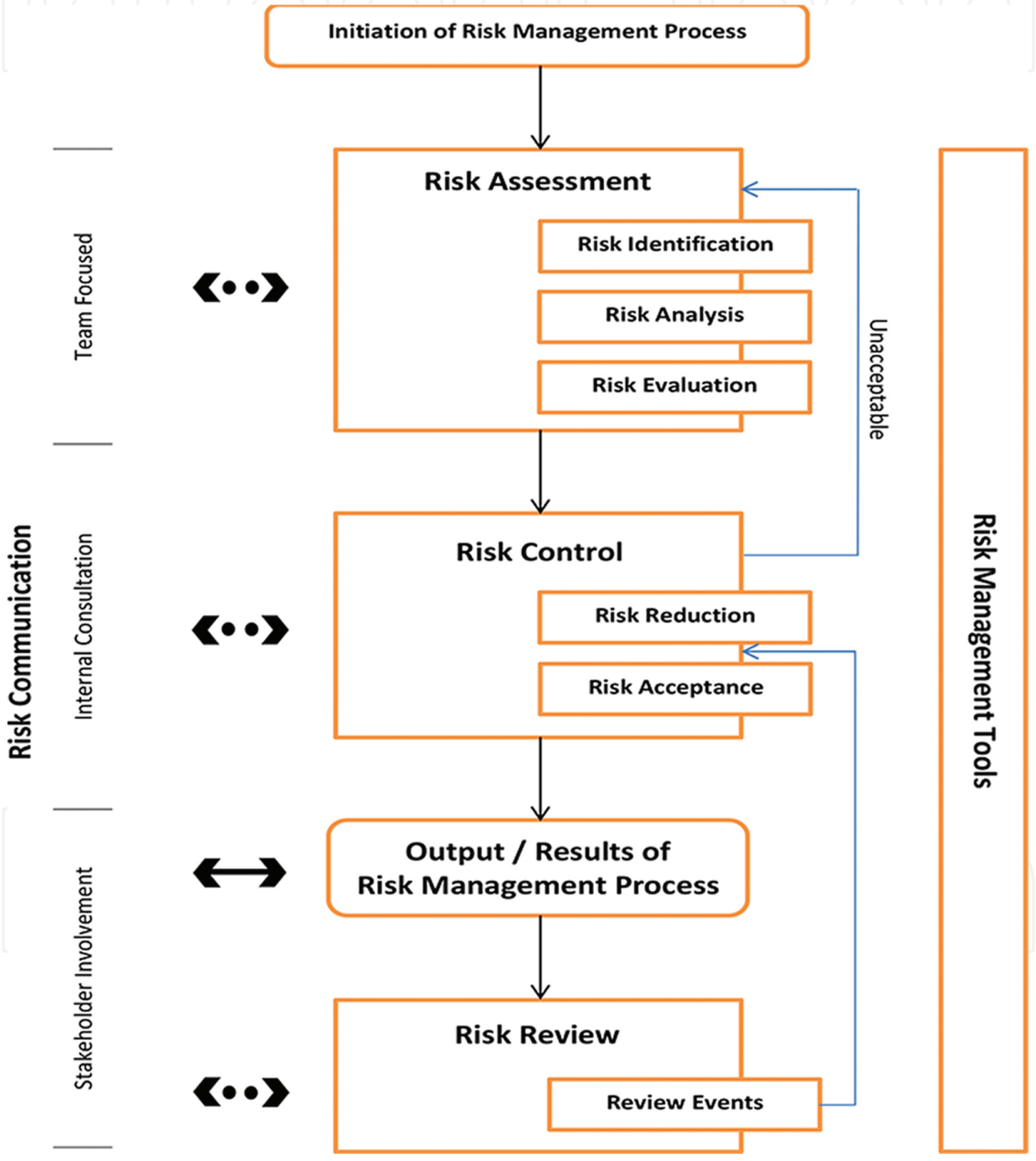

Figure 1. Flow diagram of quality risk management process [8].

ICH Q9 quality risk management provides documented, transparent, and reproducible methods to accomplish quality risk management process steps which are demonstrated in

Figure 1, based on current knowledge about assessing the probability, severity, and sometimes discoverability of the risk. According to the principle, there are two initial principles to consider in quality risk management implementation [8, 11]:

- the valuation of the risk on quality should be dependent on scientific knowledge and accordingly concerned to the protection of the patient; and
- the level of endeavor, circumstance, and documentation of the quality risk management process should be measured with the risk level of the parameter.

Still, traditional approaches like empirical and/ or internal procedures continue to provide useful information on topics such as handling of complaints, quality defects, deviations, and allocation of resources. It has been noted that the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/ or internal procedures (e.g., standard operating procedures). Some of these tools presented in the ICH Q9 guideline are given below:

- Basic risk management facilitation methods like flowcharts;
- Failure mode effects analysis (FMEA);
- Fault tree analysis (FTA);
- Hazard analysis and critical control points (HACCP);
- Risk ranking and filtering; and
- Supporting statistical tools.

It should be proper to comply with these tools for use in certain areas concerned to the medicinal material and the medical product quality. Quality risk management procedures and the adjuvant statistical implements can be utilized in combination. Combined use provides flexibility that can facilitate the implementation of quality risk management principles [8]. According to the guideline, it is important to note that "it is neither always appropriate nor always necessary to use a formal risk management process like recognized tools and/or in-house procedures" [11].

The influential quality risk management approach can further provide the high quality drug (medicinal) product to the patient for ensuring a proactive means to define and control potential quality issues during progress and production. Besides, quality risk management usage can leverage the decision making when a quality matter comes in sight. The influential quality risk management is able to support an erudite and practical approach to decision making [8]. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace proper communications between industry and regulators [11].

3.3.1. Risk assessment

A well-defined problem description or risk question is the beginning of quality risk assessment. When the risk in question is well defined, an appropriate risk management tool and the types

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of information needed to address the risk question will be more readily determined. Prior product knowledge is a key in risk assessment and consists of the accumulated laboratory, nonclinical, and clinical experience for any specific product quality attribute. It also can include relevant data from similar molecules and data from literature references. This combined knowledge provides a rationale for relating the attribute to product safety and efficacy [5].

Ishikawa (fishbone) diagram is an effective tool to capture a list of potential process inputs that impacts variation. Mapping the production process using a process flow diagram is beneficial to define the scope of the risk assessment process. FMEA or use of a prioritization matrix is helpful in identifying the process inputs that impact quality attributes [12].

For *Risk identification,* we use the information to identify hazards referring to the risk question or problem. We ask the "What might go wrong?" question, including identifying the possible consequences [8].

Risk analysis is used to estimate of the risk related with the identified hazards by some risk management tools; we can detect the harm with its role in the estimation of risk. Questions such as "What is the likelihood (probability) it will go wrong?", "What are the consequences (severity)?" must be asked to analyze the risk [8].

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions [8].

3.3.2. Risk control

Risk control decides the level of acceptance of risks which is used for risk control should be proportional to the significance of the risk including benefit-cost analysis, to understand the optimum level of risk control process which might focus on questions below:

- Is the risk above a reasonable level?
- What can be done to diminish or obviate risks?
- What is the proper balance between advantages, risks, and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction contains the actions taken to weaken the burden and possibility of harm. The application of risk reduction can introduce new risks into the system.

Risk acceptance can be a decision to accept the residual risk or it can be a decision where residual risks are not specified. For some types of harms, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to an acceptable level [8].

3.3.3. Risk review

Risk management should be a lifelong part of the quality management process. The risk management process should be reviewed to include new knowledge and experience. The

frequency of any review should be based on the risk level. Risk review might include reconsideration of risk acceptance decisions [8].

3.3.4. Risk communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process. The outputs of the quality risk management process should be documented. The interested parties might be regulators and industry, industry and the patient, industry or regulatory authority, etc. The information will cover the probability, severity, acceptability, control, treatment, discoverability, or many other aspects of risks to quality [8].

3.4. Design of experiments

While generating design space, parameters to be included or excluded to multiple variation analysis and/or model development should be assessed and selected carefully. There are significant differences between process requirements for large and small molecules, as well as differences between active substance and finished product production phases. When process parameters are defined, number of parameters for multifactorial analysis should be reduced. Generating a design space that includes all parameters that could affect the quality of a product can be long acting and exhausting. Because of this, risk analysis instruments can be used to point at parameters really affecting a CQA in the finished product [14]. Once the CQAs, CPPs, and CMAs are associated with inputs to the process, experiments can be efficiently designed to develop predictive models and confirm causal relationships, through a risk assessment [12].

In recent researches, design of experiments (DoE) has been found as a more efficient system, because it requires less experimental runs, and includes a wider "knowledge space" than traditional changing experimentation with one factor at a time. "Consequently, it is more influential in interrogating conceivable interactions between process factors, avoiding artifacts' such as empirical aggregate and work order with randomization, and making use of "hidden replication," and hereby in having better sensitivity for determining significant effects" [15]. The factors to be studied in a DoE could come from the risk assessment exercise or prior knowledge.

For DoEs with sole or poly unit operations that are used to institute CPPs and/or to define design space, the including of under mentioned information in the submission will extensively assist the valuation by the setters:

- Rationale for selection of DoE variables (including ranges) is risk assessment with alternative or different other instruments. In order to reduce the experiment load necessary for model verification or experiment design, usually it is also possible to divide parameter sets into logical groups. Working on parameters related to single unit operations can allow small groupings be made in product development [14].
- Any evidence of change in raw materials like medicinal material and/or excipients that would have an effect on approximations made from DoE studies.

- Listing of the parameters that would be kept constant during the DoEs and their individual values, consisting of comments on the effect of scale on these parameters.
- Type of empirical current design and a verification of its properness, containing the strength of the design.
- Factors under study and their ranges can be presented in a tabloid format. Supporters should figure out if the factors are abided to be measure-dependent.
- Reference to the type of analytical methods used to evaluate the data and their suitability for their intended use.
- Results and statistical analysis of DoE data showing the statistical significance of the factors and their interactions, including predictions made from DoE studies relevant to scale and equipment differences [13].

3.5. Creating design space

Design space is defined as "multidimensional combinations and interactions of input material variables and process parameters with proven assured quality." Boundaries of the design space should be very well defined. Information should be provided on which parameters and ranges are included in the design space. Comprehensive information about design of experiments and statistical methods should be included in the application [4].

In developing design spaces for existing products, multivariate models can be used for retrospective evaluation of past production data. Design spaces can be based on scientific first principles and/or empirical models. An appropriate statistical design of experiments includes a level of confidence that is valid for the entire design space, including the edges of an approved design space. Additional development knowledge and understanding contributes to design space implementation and continual improvement therefore a design space van be updated over the lifecycle. Risk assessments define the focus of development studies and define the design space as part of the risk management process. Different approaches can be considered when implementing a design space, e.g., process ranges or feedback controls to adjust parameters during processing. The design space associated with the control strategy ensures that the manufacturing process produces product that meets QTPP and CQAs all the time [13].

The design space has been instituted and verified after the process, the regulatory filing would include the reasonable ranges for all key and crucial operating parameters, and a more restricted operating space typically described for drug products. Only movement outside the DS is accepted as change, which typically initiates a regulatory post-approval change process. Activities within the DS are not considered changes [6]. The filing would contain the purified product design space at the same time, definition of the control strategy, outcome of the verification exercise, and plan for process monitoring. The filing could contain procedures in the QbD paradigm at the same time, for instance, comparability protocols or expanded change protocols, which would permit further suppleness in changes concerning preconfirmed criteria that have been complying with between the applicant and the setter [16].

3.6. Control strategy

The control strategy is "a set of planned controls, arising from existing product and process comprehension that warrants process performance and product quality. The controls can contain parameters and attributes, and it is concerned to the medicinal material and drug product materials and components, facility and equipment operating conditions, in-process controls, characterization testing, and the relevant methods and density of observation and audit, comparability tests and stability testing" [11, 15, 16].

The probability of a negative impact on product safety and efficacy can be minimized by a holistic approach to the control strategy. The aim of a control strategy for a product is to provide that influential controls are in place to pursue the risks connected with the product at a tolerable level. Therefore, the understandings of risk management and control strategy are profoundly associated and the use of risk assessment in creating the control strategy is unique to the QbD approach [16]. The control strategy creates layers of protection that reduce the risk of the hazards creating actual harm [15]. Additional emphasis on process controls should be considered in cases where products cannot be well-characterized and/or quality attributes might not be readily measurable due to limitations of testing or discoverability.

When designing the control strategy, the identification and linkage of the CQAs and CPPs should be considered. A well-developed control strategy will reduce risk but does not change the criticality of attributes. The control strategy plays a key role in ensuring that the CQAs are met, and hence that the QTPP is realized [13]. A well-designed control strategy that results from appropriate leveraging of Q8/Q9/Q10 principles leads to reliable product quality and patient-safety profiles. Design space boundaries are an integral part of a comprehensive control strategy. The control strategy for a product is expected to evolve through the product lifecycle. As product knowledge evolves and changes including acceptance criteria, analytical methodology, or the points of control (e.g., introduction of real-time release testing), there is the possibility of less reliance on end-product testing [15]. The permanent process validation is an approach which permits a firm for observing the process and make amendments to the process and/or the control strategy correspondingly. If multivariate prediction models are used in systems that pursue and update the models help to warrant the permanent convenience of the model within the control strategy [16].

3.7. Process analytical technology

There is a shift from lab-based end-product quality testing to better formulation and process design, leading potentially to more in-line, online or at-line testing.

Process analytical technology (PAT) is defined as a system for analyzing and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes during the processes. This is for the goal of ensuring final product quality. The goal of PAT is to support principles of QbD that emphasize fundamental process understanding and control focus to maximize process efficiency. The main PAT tools can be divided into two main groups as multivariate data acquisition and analysis and modern process analyzers or process analytical chemistry tools [17].

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3.8. Continual improvement

Continuous improvement is an essential factor in a modern quality system that aims developing efficiency by leveraging a process and removing wasted endeavors in production. These endeavors are being initially directed toward in order to diminish variability in process and product quality attributions.

The pharmaceutical quality system has to enable permanent development and assist to describe and implement proper product quality developments, process developments, changefulness diminution, innovations, and quality system enhancements, thus increasing the capability to fulfill quality necessities permanently. Quality risk management can be helpful for describing and prioritizing points for permanent development.

Examples of continuous improvement include actions like adjusting a set point of a process, advanced control techniques, redesigning a process step, simplifying documents, installing online measurements, changing the design space and updating the control strategy data for continuous improvement [18].

3.9. Benefits and challenges of the QbD implementation

There are of course some challenges in implementing the QbD approach like *training*, which is a major challenge; therefore, regulatory authorities and industry should conduct the training program for the implementation of the QbD concept.

It is relatively a new concept to the pharmaceutical industry and there is still a *lack of understanding and trust* among all parties so it is important to share proprietary information with especially regulatory groups.

Associated costs to implement QbD in product development, manufacturing unit operations (business and marketing decisions), different regulatory processes (BLA, NDA, ANDA, follow-on, and so on), and associated regulatory practices and culture are current concerns and establishing balance between QbD-based versus traditional demonstration of quality is in transition [17].

However, gains in the process make the implementation of the QbD indispensable. The benefits of QbD span the product lifecycle and center on areas that have the most impact to the safety, efficacy, and quality of the product and encourage innovation and continuous improvement to the product long after initial approval to leverage knowledge gained and technology advancements [3]. From the perspective of manufacturers, better understanding of product/process, development of more effective processes and less regulatory requirements are possible. In addition to these, it permits for concepts crucial and noncrucial parameters in improving design space, ensures the opportunity for centering upon significant parameters of product quality in verification works [4].

QbD provides potential opportunities for real-time quality control and reduction of the end point (QC) release testing; decreased final product testing and lower batch release costs, reduced batch failure rates; so lower operating costs from fewer failures and deviation investigations; also reduced raw material and finished product inventory costs; ensures better

design of the products with fewer problems in manufacturing; allows for the implementation of new technology to improve manufacturing without regulatory scrutiny; and ensures less complication during review, so that reduced deficiencies and quicker approval is possible [17].

Another benefit often noted is the promise of less burdensome regulatory reporting of postapproval changes. Even without the incentive of less burdensome regulatory oversight [3].

4. Quality by design approach for biotechnology products

As in past few decades, manufacturers define a process and aim to perform the process consistently in a way that the critical parameters are controlled within a narrow range in order to reduce versatility in product quality for biotechnology products. However, because the process controls are fixed in this approach, any variability in raw materials, environmental controls, and/or process operations manifests as variability in product quality and results in lot failures [19]. The international ICH Q8 (R2), Q9, and Q10 guidelines provide the foundation for implementing QbD to the biotech products, however, involve some differences and complexities [5].

A key element in implementing QbD for biotechnology products is engineering the molecule itself. A number of strategies are currently used by investigators to alter the properties of the molecule to achieve the desired balance among efficacy, stability, safety, and manufacturability. Realization of the structure and functional attributes of therapeutic proteins, including monoclonal antibodies (MAbs), is crucial to create the design space, because that understanding facilitates the selection of requested quality attributes through the molecular design while ensuring that bioactivity of the protein therapeutic is maintained [5].

There is a need for certain technologies and processes for QbD implementation in the biopharmaceutical industry. Extensive data about the product and its manufacturing process is required for QbD implementation. It is not possible to evaluate the effect of every variable numerous variables and attributes that show interaction to impact safety and efficacy of a biotechnology product. Statistical approaches, such as DOE and multivariate data analysis (MVDA) along with risk management tools, can help to ensure that resources are spent on the most important tasks [19]. Currently, authorities have not submitted the clear guidance on what they take into consideration to be a reasonable risk for biotechnology products. The industry is able to work with health authorities for sharing examples of process changes and to ensure an evaluation for postapproval variations and notification categorization. There is no clearly defined mechanism to share process understanding for well-understood processes and products [3].

According to information given above, basic QbD approaches for biotechnological products and their manufacturing are QTPP and CQAs. Because of unique nature of the bioproducts/bioprocesses, multivariate QTTP parameters are at stake. For this reason, QbD approaches for monoclonal antibodies will be considered in the chapter.

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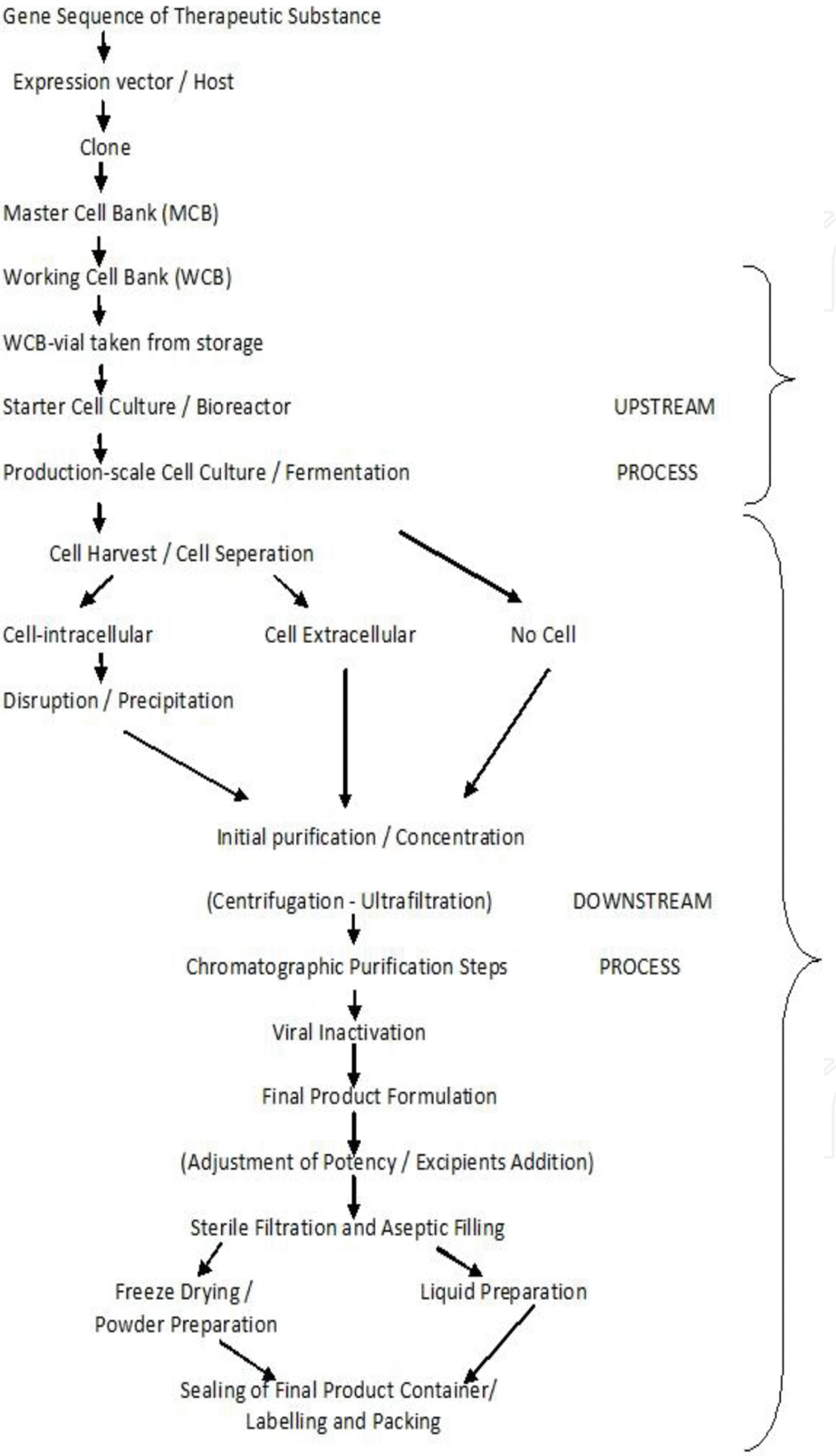

Figure 2. Standard production process flow diagram (biotechnological products) [20–22].

In **Figure 2**, basic bioprocessing steps are given for better understanding of QTTP and CQAs for biotechnological products. In the downstream process, various purification methods are integrated as seen. Selection of one of the chromatographic methods given in **Table 1** depends on the drug substance characteristics, cell line and bioreactor choices, and other process-related properties.

Chromatographic method	Principle
Size-exclusion (Gel-filtration) chromatography	Size/shape difference
Ion-exchange chromatography	Net surface charge difference, pH
Affinity chromatography	Biological affinity between drug substance and ligand (metal chelates, lectins, dyes)
Hydrophobic interaction chromatography	Surface hydrophobicity difference, polarity
Immunoaffinity	Purification of Mab, based on affinity between Mab and antigen (protein A, protein G)
Hydroxyapatite chromatography	Complex interaction between drug substance and media
İmmobilized metal-ion affinity	Metal-ion binding
Chromatofocusing	Isoelectric point difference

Source: [20, 22, 24, 26].

Table 1. Types of chromatographic methods used in downstream process of biotech products.

In downstream processing of Mabs, purification steps are similar to the other biotech products but also contain specific methods such as protein A chromatography which is commonly used for its IgG (Mab) affinity. This method distinguishes itself by high selectivity toward IgG-type antibodies, high flow rate, and capacity [20, 23–25].

In large-scale production of biopharmaceuticals, there are optimization criteria for bioprocess development; concentration, volumetric productivity, yield (high titer), and quality (sequence, purity, glycosylation pattern, activity). Optimization begins with identification and characterization of the drug molecule as well as its mode of action. In the light of this information; cell culture processing (cell engineering, production cell line selection, type of bioreactor and critical parameters, feeding strategy (batch, fed-batch, perfusion, continuous), downstream process steps and parameters, process monitoring, analytics and formulation studies) is designed in compliance with regulatory requirements [22, 24, 27, 28].

In terms of identification and characterization, monoclonal antibodies (Mabs) can be considered as an example for drug-substance properties. Mabs are produced by hybridoma technology and its basic concept is producing identical antibodies and simply includes these steps [20, 29]:

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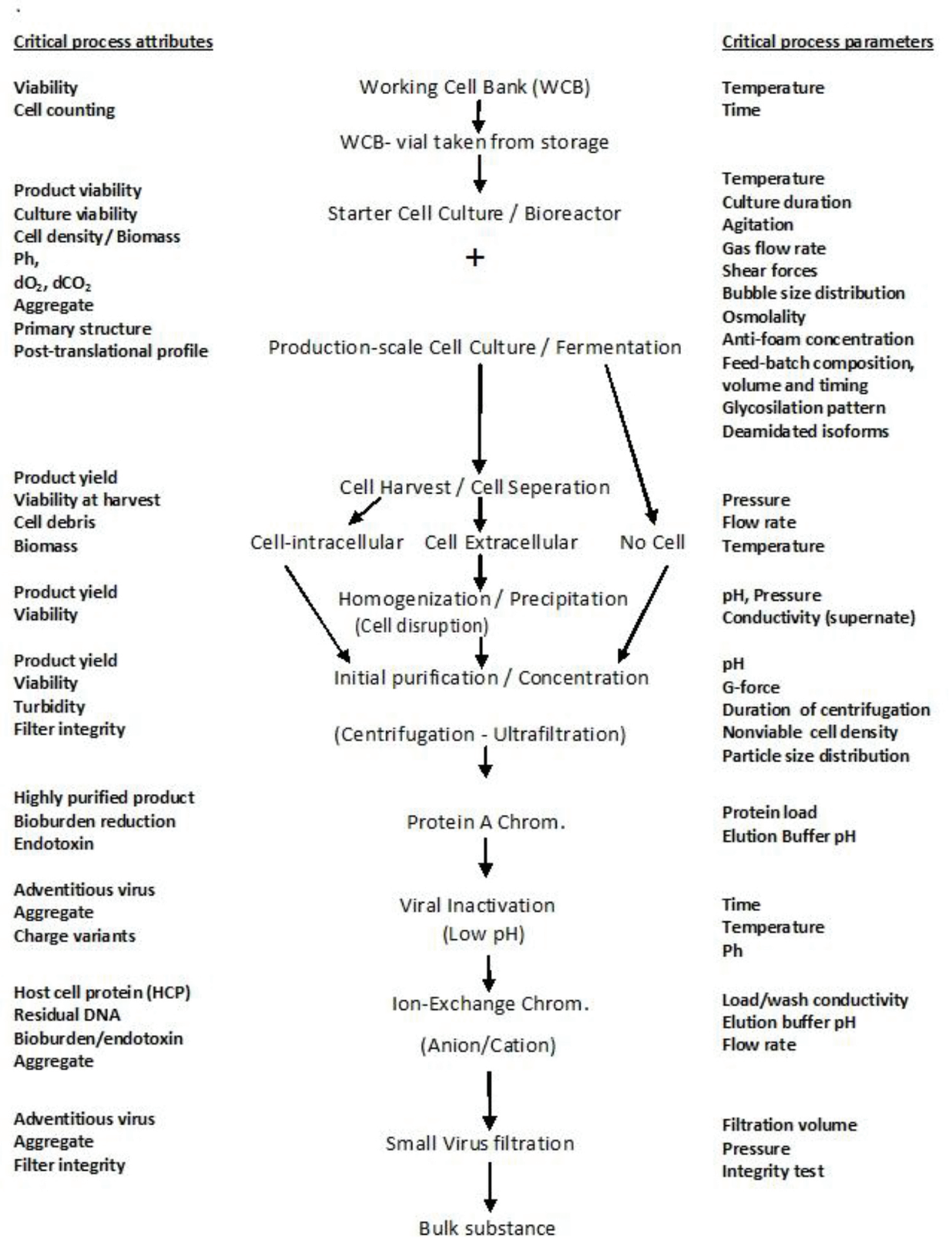

Figure 3. Control strategy for upstream and downstream processes of biomanufacturing. dO_2: dissolved oxygen, dCO_2: dissolved carbon dioxide [22–27, 30–34].

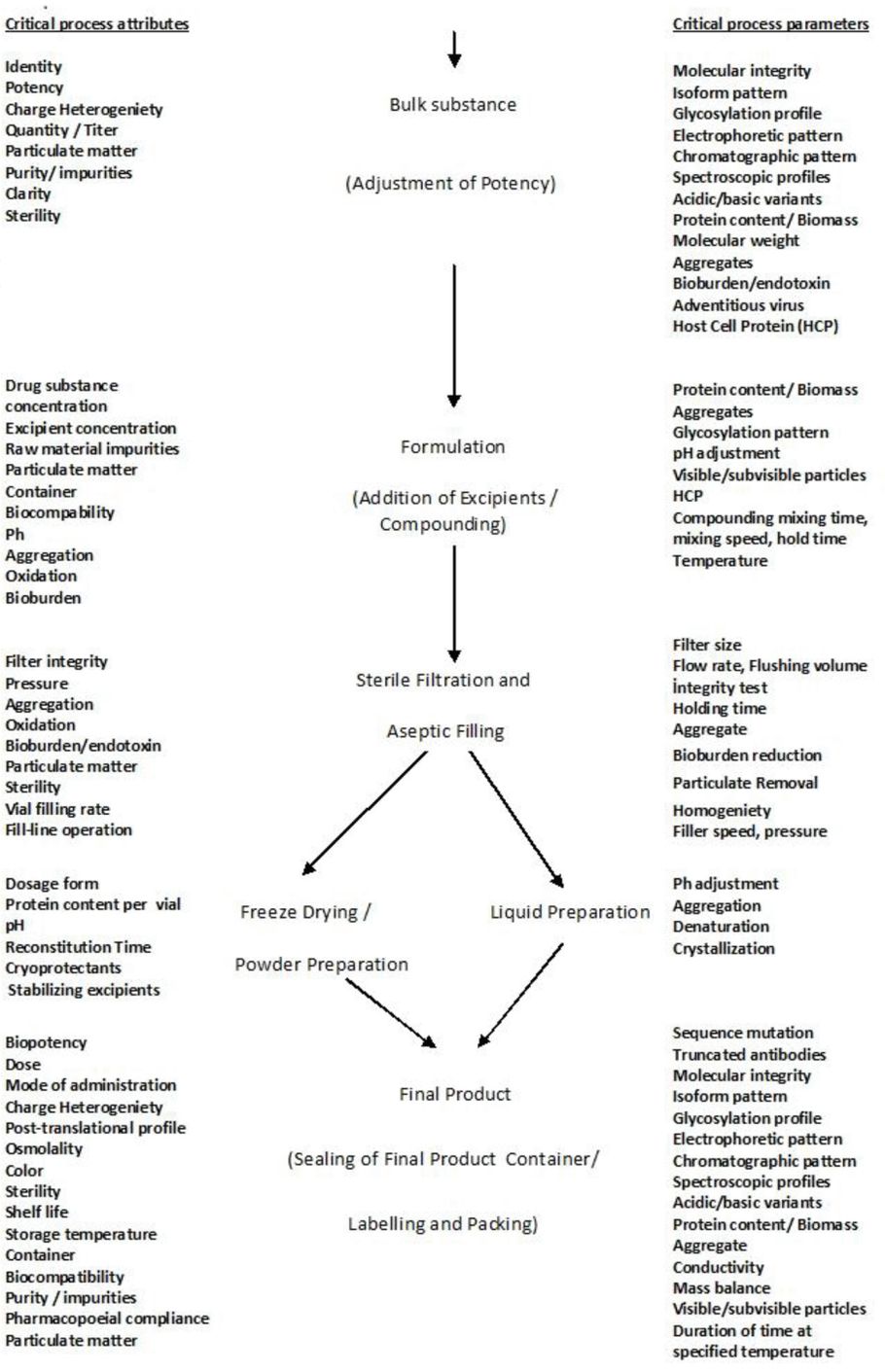

Figure 4. Control strategy for drug substance and final product processes [22–27, 30–34].

- immunization of mouse with antigen
- isolation of B cells (contains antibodies)
- cell fusion with myeloma cells (immortal B cell cancer cells)
- screening and selection of hybrids and propagation

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- selecting positive clones, freezing the clones
- production of ascites and harvest specific antibody

Mabs consist of constant Fc regions and constant/variable Fab regions. Fc regions have heavy chains, while Fab regions have both heavy and light chains. The Fc region is responsible for biological activity. Variable light chains (VL) of the Fab region are responsible for antigen recognition and binding. There are four types of Mabs used for therapy; murine, chimeric, humanized, and human Mabs. Murine Mabs consist of overall murine amino acids, while chimeric Mabs' only variable regions are murine originated, humanized Mabs' complementarity determining regions (CDRs) are murine originated, and human IgG consists of entirely human amino acids [29].

Humanized and human Mabs are preferred for their reduced risk of heterogeneity and negative impact on bioactivity. Determination of critical attributes and parameters for Mab products depends on overall structure of Mab, cell clone, and media. Complementarity determining regions (CDRs) of the heavy and light chains have potential glycosylation, deamidation, and oxidation sites, which pose risks such as undesirable glycosylation profiles, disulphide bond formation, and oxidation [29].

Product heterogeneity is a common problem for all recombinant biotechnological products as well as for Mabs. This could occur either in cell culture process or downstream process and eliminating these variants all along manufacturing process is one of basic approaches of QbD. These variants such as aggregates, deamidation and oxidation products, and different glycosylation patterns strongly affect product's quality, potency, bioavailability, and immunogenicity which could be fatal. In **Figures 3** and **4**, key process attributes and related critical parameters are outlined in parallel with biomanufacturing steps and further information is given within the article [29].

Cell line, bioreactor, and medium selection and design are based on cell culture process approaches. Control strategies of pH, oxygen (O_2), carbon dioxide (CO_2), temperature, and pressure are determinant for optimization and scaleup [27]:

- pH control strategy; basically based on correlation between CO_2 addition and base addition which is related to osmolality, pH, and CO_2.
- O_2 control strategy; depends on agitation, gas flow rate, and orifice diameter which is related to dO_2, dCO_2, shear forces, mixing, and bubble-size distribution.
- temperature control strategy; based on temperature, which is related to O_2 and CO_2 solubilities.
- pressure control strategy; based on pressure, which is related to O_2 and CO_2 solubilities.

According to these attributes, physical parameters such as gas flow rate, agitation speed, shear stress; chemical parameters such as dO_2, dCO_2, pH, osmolality, and by-product and substrate metabolites and biological parameters such as cell viability and concentration are critical parameters for the cell culture process. Even minor variations in these parameters could have very strong impact on productivity, product quality, and potency. Thus, these parameters must

be characterized and optimized. Some of these parameters are measured by direct connection to the operator but some need to be measured via intervention. For example, viability is measured through cell counting tests such as hemocytometer [27].

Before selecting the cell line, small scale production of chosen cells (*Escherichia coli*, yeast, insect cell, mammalian cells) are carried out and the cell with best performance in terms of activity, speed, and solubility is selected for large-scale production. Post-translational processing and stable expression are critical parameters for selection. For example, mammalian cells (CHO, mouse myeloma cells) have closer glycosylation pattern to human and ensure stable expression, thus these cells are commonly used for Mab production [24, 27, 35].

Bioreactor and culture media selection and design approaches should meet defined product quality, productivity, and cell-line specifications. Bioreactor is operated by batch, fed-batch, or continuous modes and the choice of bioreactor based on two criteria; productivity and sterility. Continuous systems ensure high productivity but cleaning is a matter of fact. Disposable bioreactor systems seem to be a good alternative for production; however, they need to be optimized. Critical parameters for design strategy are; reactor type, mixing, temperature, density, shear stress, gas exchange (O_2-CO_2), perfusion rate, and ease of cleaning [24, 27].

Commonly used cell culture medium supplements consist of glucose, amino acids, inorganic salts, vitamins, growth factors, and animal component free hydrolysates. However, medium ingredients vary due to the high diversity of cell culture properties and medium optimization becomes compulsory for optimal growth of the culture [24, 27].

Basic approaches of the feeding strategy are; maintaining culture viability, promoting growth, increasing productivity and cell density, cost, and time-effectiveness for industrial-scale production. This requires optimization of feed composition in a timely manner and balancing between nutrient consumption and by-product accumulation (ammonium lactate) which is specific for individual cell lines. Combination systems with high-throughput screening and/or statistical design of experiment (DOE) approaches provide ideal formulations for achieving the maximum cell growth and volumetric productivity. Using anti-apoptotic molecules is another approach for prolonging cell viability to increase productivity [24, 27, 36, 37].

Optimization approaches in downstream processing (DSP) are; yield, purity, productivity, larger process capabilities, and faster process development. DSP based on various filtration and chromatographic operation units, which consist of viral-inactivation and final sterile filtration steps. Removal of contaminants and impurities such as residual cell, media components, host cell protein (HCP), residual DNA, product variants, adventitious viruses, endotoxin, aggregates, and other process related impurities is very crucial for producing products suitable for human use. Among other impurities; product variants, aggregates, and host cell protein (HCP) are most important in activity, efficacy, or safety aspects. First purification step is recovery of the drug substance from cell culture and removal of cell/cell debris, fluid. This process is operated by centrifugation/ultrafiltration and if needed microfiltration steps. These steps are determinant for success of further purification process. Chromatographic steps are critical for high degree of purity and recovery. Design of ligands/matrices of chromatographic

methods should be optimized for shorter residence time, higher flow rates, and longer lifecycles, which results in increased binding capacity and improved removal of impurities in washing steps. Primary critical parameters for optimization are; viability, yield, aggregates, isoforms, HCP, residual DNA, and turbidity. Most of the overall manufacturing costs derive from downstream processing and increase in parallel with higher yield. The main approach for integrating purification steps is increasing titer with cost-cutting measures. Process development is achieved by PAT-QbD systems, high-throughput screening, continuous processing, small-scale/parallel facilities, and integration of modeling [22, 24–26, 30, 31, 34].

Quality attribute	Analytical assay	Quality assessment criteria
Molecule integrity/ weight	PM/MS, cDNA sequence, IEF, CE-SDS or SDS-PAGE	Amino acid sequence/antibody mutation
Biopotency	Immunoassay, biological activity tests	Target antigen binding affinity
Color, clarity	Colorless, clear	
Aggregation/fragments	HP-SEC, electrophoresis	High levels of aggregation, risk of immunogenicity
Glycosylation	HPLC or CE based glycan assay	High levels of different glycosylation forms
Charge heterogeneity	IEF, ion exchange chromatography, or HPLC	High levels of acidic or basic variant/peaks
Process-related impurities	Immunoassay, DNA-hybridization, Q-PCR, electron microscopy, *in vivo/in vitro* assays, spectral analysis	Avoid HCP, leached Protein A, DNA, viruses, cell culture medium proteins
Particulate matter	Visible/sub-visible particles USP	Meet USP 788 requirements
Bioburden/endotoxin	LAL test	Meet USP 85 requirements
Thermal stability	DSC	According to specified temperature

CE, capillary electrophoresis; IEF, isoelectric focusing; SDS-PAGE, sodium dodecyl sulphate polyacrylamide gel electrophoresis; HP-SEC, high-pressure size exclusion chromatography; PM/MS, peptide mapping-mass spectrometry; DSC, differential scanning calorimetry. *Source*: [25, 27, 28, 30, 31, 38].

Table 2. Drug product specifications in biotechnological manufacturing.

Drug product quality attributes and criteria are given in **Table 2** and the main goal of the QbD design is to match these criteria and guarantee defined quality for drug product at the end of the manufacturing process. At this point, process monitoring by biosensors is very critical throughout manufacturing. Especially monitoring of biomass and cell volumes is the most important. Primary physical, chemical, and biological parameters monitored by sensors are genetic/metabolic analysis, biomass/viability, product characteristics, product concentration, impurities, temperature, osmolality, nutrients, metabolites/substrates, pH, dissolved O_2, volume/weight, CO_2 rate, flow pressure, stirrer speed, viscosity, and side components. Also,

biosensors should match some criteria in order to be valid for quality assurance; such as robustness, reliability, accuracy, reproducibility, analysis frequency, selectivity, sensitivity, linearity, ease of cleaning, and sterility [26, 28, 35].

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