SUMMER 2014 • Volume 13/ Issue 2 • ISSN 1538-8786

BioProcessing JOURNAL

Trends & Developments in BioProcess Technology

A Production of BioProcess Technology Network

BioProcessing JOURNAL
TRENDS & DEVELOPMENTS IN BIOPROCESS TECHNOLOGY

Using Quality by Design (QbD) to Build Effective Product and Process Control Strategies Based on a Well-Structured Design Space

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Abstract

This article proposes a "design space" structure for using Quality by Design (QbD) to develop processes and control strategies for developing and manufacturing biopharmaceuticals.

Introduction

One goal of developing a manufacturing process is to manufacture a product that always meets the quality target product profile with minimum variability. To accomplish this goal, the approach used to develop biopharmaceuticals must provide effective process and product control strategies. ICH Q11 defines a "control strategy" as:

> ***Control Strategy:*** *A planned set of controls derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.*[1]

While the Q11 definition includes all aspects of manufacturing drug product for the patient, this article will focus on the manufacturing process to produce drug substances. However, the principles discussed are widely applicable to all phases of manufacturing complex products, including biopharmaceuticals.

The ICH Q8 "design space" is a formal description of the process, and all the process's elements and their interrelationships in the definition of control strategies.

The "design space" is defined as:

> ***Design Space (DS):*** *The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.*[1-3]

Basically, the design space (as described above) is a model of the process. The design space definition has two parts. The first sentence is the definition, while the rest of the paragraph clarifies the definition by stating regulatory requirements and its subsequent treatment by regulatory agencies. The policy statements require that the model be precisely defined and clearly stated. Many of the modeling methods that must be used are difficult to develop to the point where they adequately support these requirements. Thus, the burden of developing an effective and usable design space requires that it be structured appropriately to provide understanding and guidance for the representation of the process's behavior, performance, and control strategies.

Using "Quality by Design" (QbD) during the design stage of the process validation lifecycle is essential to creating effective control strategies.[2,3] The process validation lifecycle, as described in the 2011 FDA guidance documentation, is shown in Figure 1.[3]

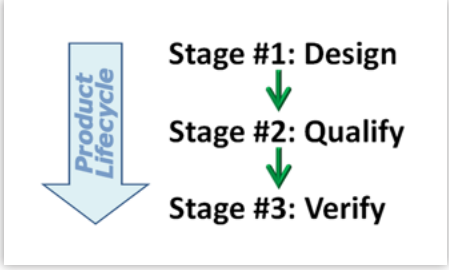


FIGURE 1. A summary of the FDA's process validation/ product lifecycle paradigm.

FDA's process validation paradigm is an effective foundation for understanding the development of biopharmaceuticals. If the paradigm is expanded, as shown in Figure 2, to more effectively cover the entire development and manufacturing lifecycle, the Quality by Design tool can be effectively incorporated.[4, 5]

The QbD paradigm addresses the issue of identifying and resolving the problems that will be encountered when the qualification and operating stages are reached. The question becomes: *How can future problems be anticipated before the process is completed and implemented?* Drawing from the experience of other fields, particularly operations research (OR), the answer is the use of models that simulate or represent the process.[6, 7] For biopharmaceuticals, the design space described above is the model for developing and understanding the process's behavior and designing the control strategies required to assure that the manufacturing process consistently produces quality product.

Figure 3 further clarifies the relationship between QbD, the design space, and the control strategies. The initial iterations of the QbD loop may be focused on building an early conceptual design space based on subject matter expert (SME) and/or mathematical models. Small laboratory-scale experimental models may also be used to define the process's behavior and identify important parameters. As the QbD loop is iterated, the scale may increase as further experimental data is collected, understood, and used to build successively more complex and complete models of the process. Eventually, even full-scale models may be used during engineering runs to further refine process understanding and the resulting design space to achieve the requirements stated in the regulatory design space definition. At some point, the process will be deemed to be ready, and the full-scale manufacturing process assembled for passage to the qualification stage.

Because the design space is so important, additional understanding of the design space and how it is used within the QbD loop is important. In Figure 4, additional items are added to the QbD loop.

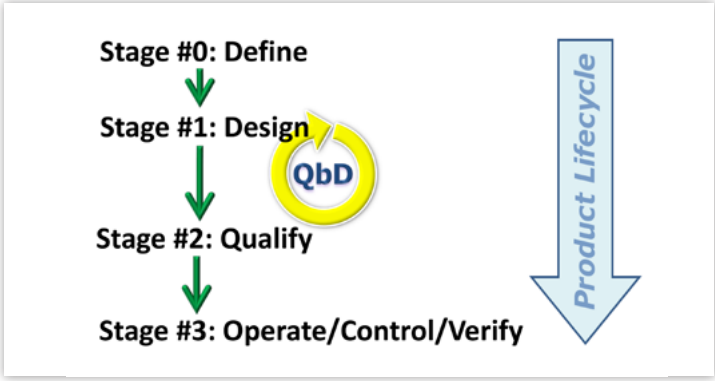


FIGURE 2. The expanded process validation paradigm is shown. QbD is the process development and risk modification tool that minimizes qualification and operational risks.

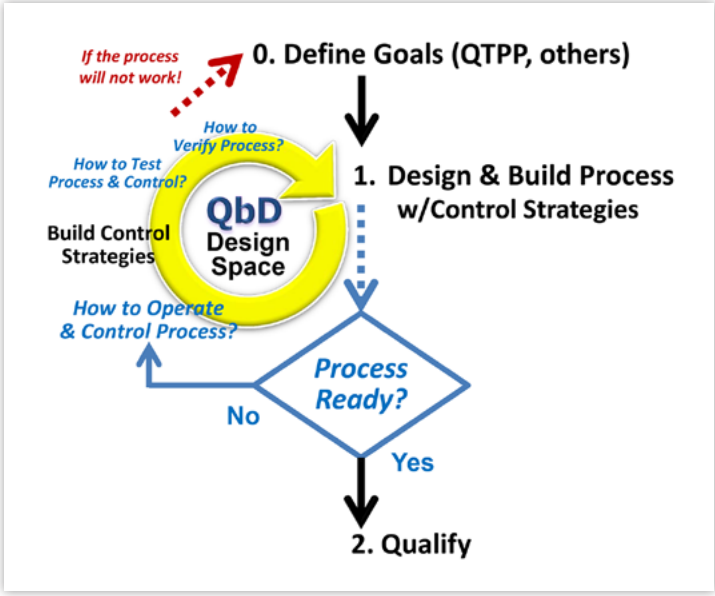


FIGURE 3. QbD is a feedback loop which asks the questions and identifies the issues and problems that will eventually be encountered during the last two lifecycle stages.

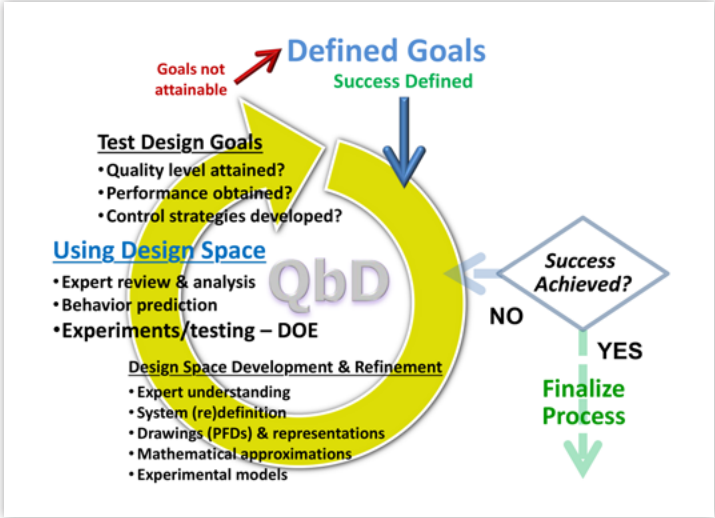


FIGURE 4 (right). The QbD loop starts by assembling a model that represents an understanding of the process. The QbD paradigm then uses the modeling methods shown, including process understanding, to predict the performance and behavior of the process. The final element of the QbD cycle is to test the model against the required performance and control goals. If the goals are met to the extent reasonably possible, then the process is finalized, implemented, and formal Stage #2 qualification begins. Otherwise, the QbD loop is repeated to refine the model and repeat the design stage testing and review.

With the role of the design space established in the development of control strategies, we turn to further refining the structure of the design space. The design space is complex and needs to be broken down into elements that permit various individual control strategies to be developed for assembly into the overall process and product control strategy required to effectively control overall product quality to the patient.

Developing a Design Space Structure

An important part of building good design spaces is having a model structure that clearly defines the elements required to characterize all the process input and outputs so that good control strategies are developed. Figure 5 depicts the input and output structure implied by ICH Q8. ICH Q8 contains the following definitions:[2]

> ***Critical Process Parameter (CPP)*** *– The parameter whose variability has an impact on the critical quality attribute, and therefore should be monitored and controlled to ensure the process produces the desired quality.*
>
> ***Critical Quality Attribute (CQA)*** *– 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.*
>
> ***Quality Target Product Profile (QTPP)*** *– 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 product.*

The above definitions do not clearly delineate whether either CQAs or CPPs are inputs or outputs. The consensus definition of CQAs seems to be that it represents an attribute of the product's quality and as such, would be an output of the process. CPPs, on the other hand, could represent either an input or an output of the process, as defined above. In the development of control strategies, outputs that must be controlled have to be clearly defined along with the process inputs that are manipulated to control the process's behavior and performance.

Another important concept, particularly for biopharmaceuticals, is that the QTPP contains both known and unknown CQAs. Both impact the patient and must be controlled to make a therapeutic consistently safe and effective. Because many of the CQAs of the product are unknown, the variability of all aspects of the process must be minimized in order to indirectly control the unknown CQAs. The product is, to some extent, controlled by measuring the known CQAs through end-product QC testing to assure compliance to specifications as a means of controlling the product. Effective control of the process to minimize process variability is the only method of controlling unknown CQAs.

Defining Process Outputs

To more effectively control all aspects of the process, we will examine the process outputs in more detail. In order to effectively control a process, critical outputs must be measured in real time to control a process's performance using feedback control systems. Most CQAs are complex and difficult to measure and thus, not available for on-line measurement. In addition, the process may have output responses that are not necessarily a direct measure of the product's quality, but still important with respect to controlling the behavior of the process. This second set of outputs, as shown in Figure 6, will be called "critical process responses" (CPRs). Note that we are basically changing the name of "critical process [output] parameters" to "critical process responses" in order to clearly separate inputs and outputs. Attributes and responses will be delineated as "outputs" and "parameters" as inputs. The following is a definition of a CPR:

Critical Process Response **–** A process output, or response, that reflects the behavior or performance of the process. CPRs are modified by changes in the process inputs. CPRs may be measured on-line and may be available for use in automated process control systems. A CPR may or may not be a CQA.

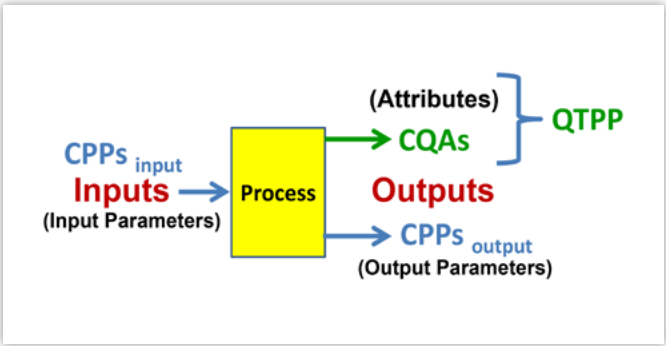


FIGURE 5. The current regulatory lexicon for process inputs and outputs. Product related outputs are called CQAs that collectively form the QTPP. The process inputs and outputs are CPPs.

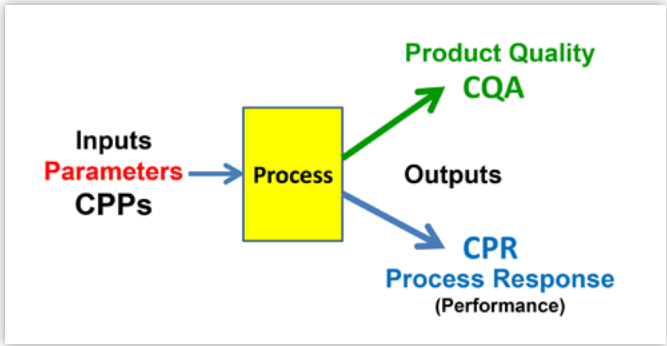


FIGURE 6. The outputs of the process can be broken into quality (product) attributes and process responses. The first, CQA, describes the quality of the product. The second, CPR, reflects the performance or response of the process to changes in the CPPs.

To control the QTPP, both the CQAs that reflect the product quality and CPRs that reflect the process's performance must be included in the design space to properly model the process to meet the regulatory definition. In some cases, a CQA that can be easily measured can also be a CPR. A CPR may or may not have a significant impact on both known and unknown CQAs of the QTPP. The discussion now turns to characterizing the input CPPs.

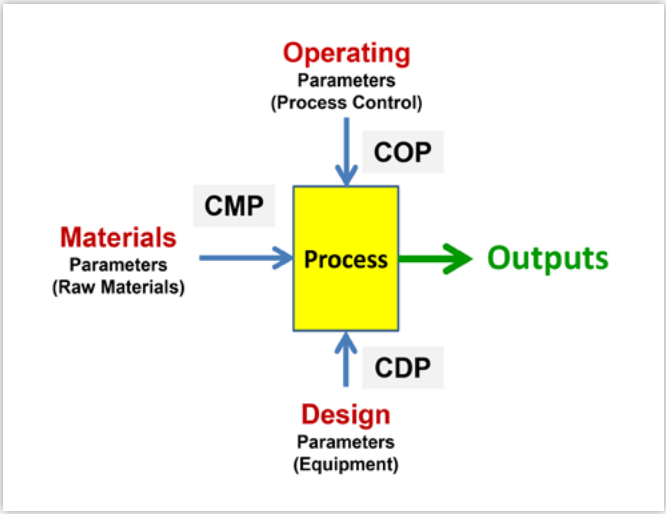
Defining Process Inputs

In order to control a process, the inputs to the process must be identified, characterized, and controlled. The key to understanding the process's inputs is to think in terms of control strategies for the various types of inputs. If all biopharmaceutical process inputs are evaluated, they fall into three categories. Each category is controlled by a specific control strategy. The three categories are divided into groups, as shown in Figure 7.

While all three categories of parameters impact the performance of the process, each category requires very different control strategies. Specific definitions for the three categories are:

Critical Material Parameter (CMP) – CMPs are the raw materials required to supply the process with ingredients. In some cases, these are referred to as critical material attributes. Critical material attributes (or outputs) of one process become the critical material parameters (an input) of the next process. Examples of CMP are media and gases to a bioreactor, or buffer materials to downstream processes. Control of CMPs requires several approaches from vendor audits and in-coming QC testing to screening assays. Variability of CMPs is a frequent source of control problems with biopharmaceutical processes.

Critical Design Parameter (CDP) – CDPs are defined by the equipment selected to operate the process. Once selected, they typically do not change except through modification of the equipment to achieve some desired change in the process's performance. CDPs are controlled through a formal engineering change control program.



Critical Operating Parameter (COP) – Critical operating parameters are CPPs that can be adjusted during operation. Some COPs are held constant at levels defined during process development. Other COPs are available to actively control process behavior using feedback loops. Of note is that downstream buffer composition is a COP, in contrast to the actual materials used being CMPs.

During process development, the CMPs and CDPs are defined and, to the extent possible, fixed and placed under their own control strategies to keep them from changing. Both are available for continuous improvement opportunities, but for the current discussion, both will be considered fixed. The discussion now turns to the third input category, COPs. Some operating parameters can be measured on-line and determined during process development to have a significant impact on a CPR or CQA and must be controlled. We call these COPs "critical control parameters" (CCPs). We will use the following CCP definition found in ASTM E2476:

> ***Critical Control Parameter (CCP)*** – *". . .that subset of Critical Process Parameters which can be changed under automated control to modify the trajectory of the process, and hence to modify the CQAs of the intermediate process product or the final drug product."*[8]

The identification of CCPs—and selecting which CCPs are fixed at a particular value—and which will be used to actively control the process is a primary goal of process development and engineering. To develop a process control strategy, the CCPs must be paired with the appropriate CPR.

Developing Product and Process Control Strategies

The process control requirements for product control is the basis of FDA's 2011 process validation guidance. The principles of process measurement and control are given in FDA's guidance on Process Analytical Technologies (PAT). That guidance defines PAT as:

> ***PAT*** – *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.*[9]

The definition includes measurement and control of both the CQAs and CPRs (discussed earlier). The concept

FIGURE 7. The three input categories are material inputs associated with raw materials (CMP), design parameters associated with the design of the equipment (CDP), and operating parameters adjusted during development or controlled during the process's operation (COP).

of controlling the process to assure product quality for releasing final product is stated in the following Q8 definition of "real-time release testing" (RTRT):

> ***Real-Time Release Testing (RTRT)–*** *The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls.*[2]

All of the concepts discussed above can be integrated into a single design space structure. The elements of that structure are depicted in Figure 8.

The design space is composed of process input, outputs, and control strategies. The goal of the control strategies for the CPRs, CCPs, QC measurement of CQAs, and the RTRT process control results in a good overall product control strategy for the release of final product. To further examine the underlying design space concepts, a simplified bioreactor example will be reviewed.

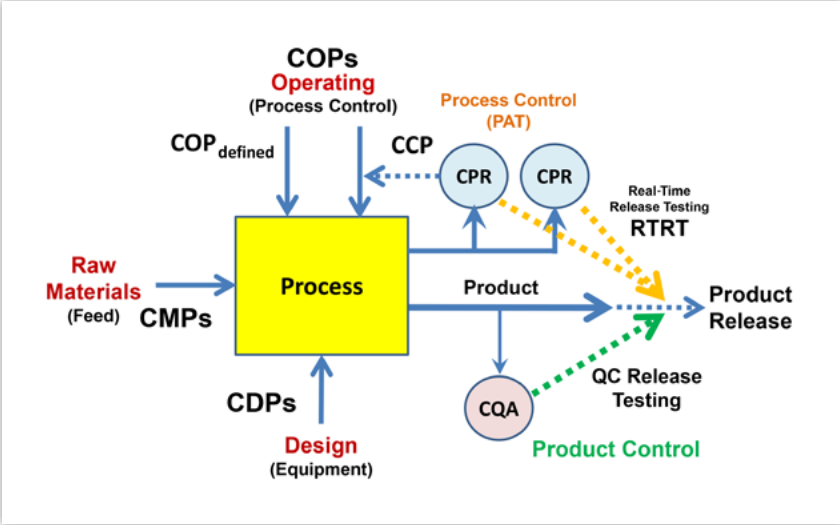


FIGURE 8. The product control mechanism of QC release testing and the RTRT mechanism implemented through the measurement and control of the CPRs. RTRT would include monitoring of CCPs as well as other important COPs. Note that a CPR may also be a CQA. Some CPR ranges are defined during process development, while other CPRs are used to implement automatic control by manipulating CCPs in feedback control loops designed during process development as part of the process's control strategy.

Simplified Bioreactor Example

The outputs of a bioreactor are shown in Figure 9. Both the CPRs and CQAs are shown. The bioreactor is a simple, agitated/stirred tank reactor. However, any bioreactor type could be used.

Many of the CPRs have a direct impact on the CQAs. For example, the viability of the culture, a CPR, has a significant impact on host cell protein (HCP) content, protease levels, *etc*. Of course, the final value of many of the CQAs in the drug substance is determined by the downstream processes that purify the media coming from the bioreactor. However, controlling the upstream challenge to the downstream process is essential to assure that downstream processes reliably produce final product that meets final product release specifications.

Some of the CPRs shown are controlled by feedback control systems that measure the CPRs and control CCPs to keep the CPRs at target values. Because the CQAs are typically very hard to measure, the emphasis of the bioreactor control strategies is to tightly control as many of the CPRs as possible.

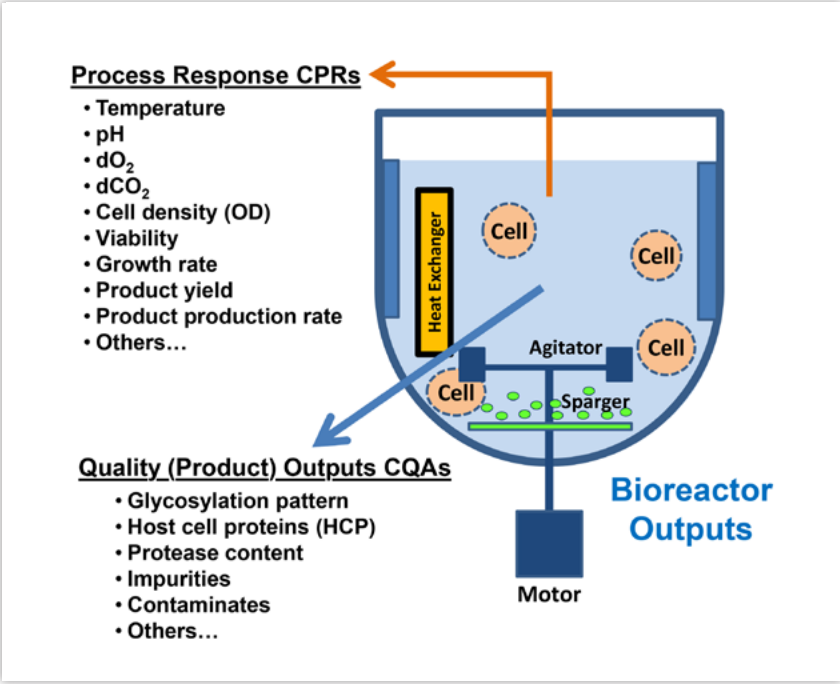


FIGURE 9. Bioreactor outputs are divided into the CQAs and CPRs. CQAs are critical attributes of the product sent to the downstream processes. CPRs are critical response outputs of the bioreactor's performance during operation.

The inputs for the bioreactor are shown in Figure 10. All three types of input parameters are shown. The design parameters (CDPs) are ultimately fixed, based on process requirements in the final process, but may be subject to adjustment and experimental study during process development. Once fixed, CDPs are controlled using an engineering change control mechanism that controls the design parameters as well as various maintenance requirements to assure that the CDPs remain constant during the operational lifecycle.

Raw material parameters (CMPs) include all the raw materials added to the bioreactor. The control strategy for CMPs includes QC incoming raw materials testing, QA vendor control systems, and other quality systems required to assure that all raw materials do not change from the parameter targets defined during process development.

The third type of input parameters, operating parameters (COPs), can be manipulated during operation. Many of the COPs, such as media composition, are fixed during process development. Other COPs or CCPs are manipulated based on measuring CPRs. For example, the harvest time may be determined by the final cell density, as measured by the cell density of the culture. Other CPRs may be controlled using automated feedback loops. For example, pH can be adjusted by acid and base addition, and temperature by manipulating coolant flow rate.

Worth noting is that temperature appears as both a CPR (an output) and as a COP (an input). Temperature can be either, depending on how the system boundary is defined.

System Definition

In Figure 11, two system boundary definitions are shown. In the wider process definition, temperature is an input because the temperature control system is inside

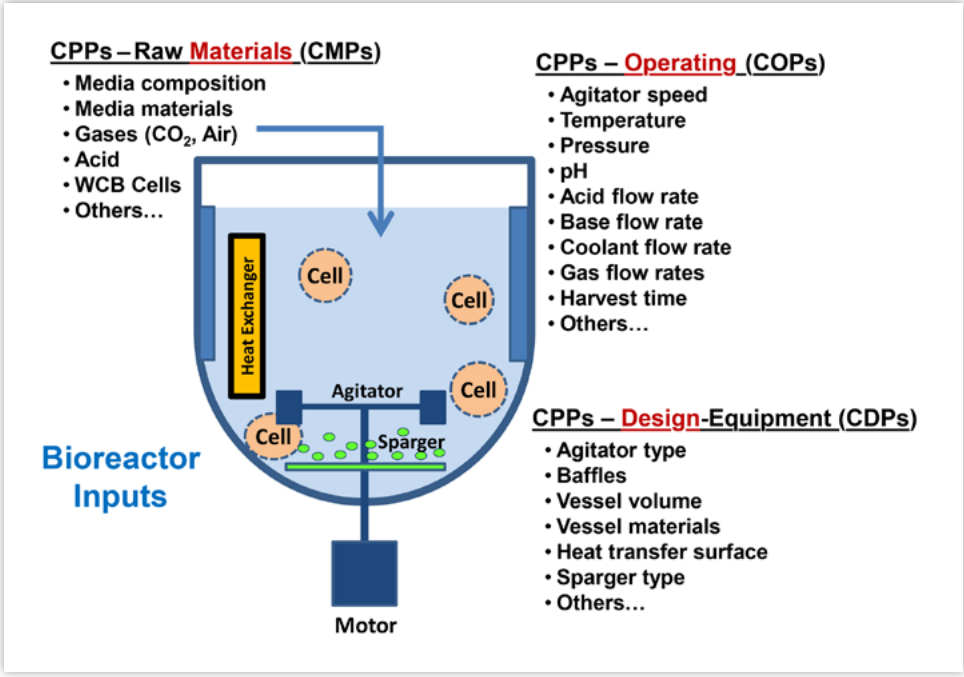


FIGURE 10. Bioreactor CPPs broken out into the three categories.

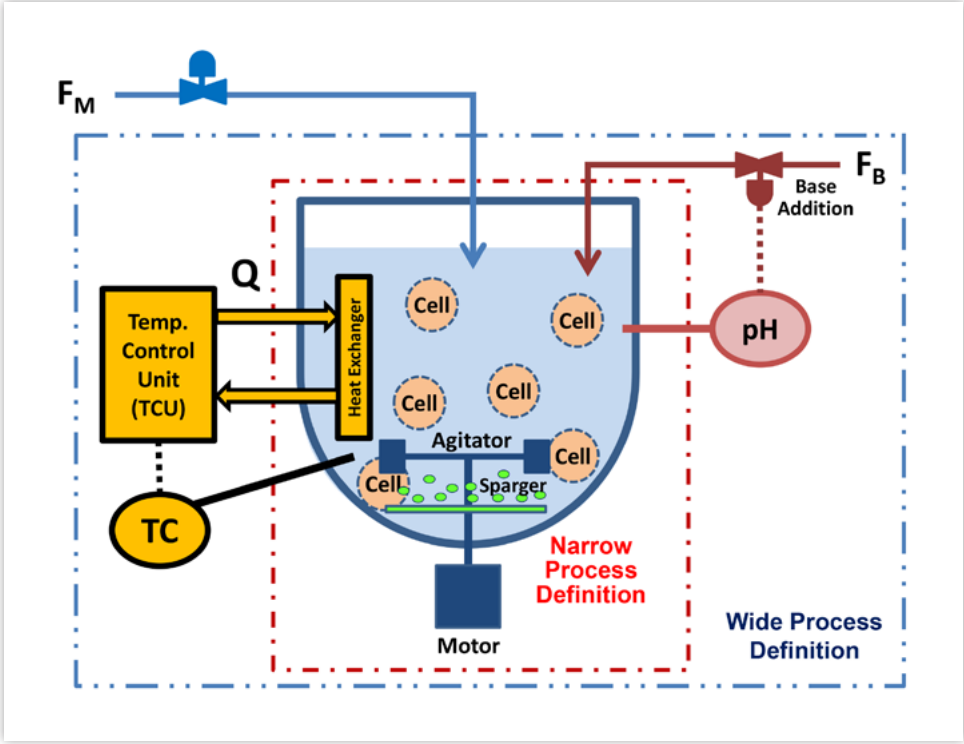


FIGURE 11. How the process systems are defined impacts the classification of some inputs and outputs. The narrow definition shown would make both pH and temperature CPRs, while the wider system definition would make both COPs.

the boundary and thus, included. This boundary would be appropriate if the temperature control system is capable of precisely controlling the temperature for all situations the process may experience. If, on the other hand, the bioreactor is challenged by significant energy outputs (*e.g.*, fermentation) from the process, temperature may be difficult to control. In that case, the process boundary should be more narrowly defined to make temperature a CPR while pairing it with the coolant flow rate as the CCP in a feedback control loop.

To define the bioreactor's design space, Figures 9 and 10 are combined with the structure proposed in Figure 8. With all the inputs and outputs placed in the various categories, the "Stage #1: Design" activities can begin defining the performance of the bioreactor as a function of all the input parameters (CPPs). During the establishment of the bioreactor's product and process behavior and performance, appropriate control strategies can be assembled for all the inputs and outputs required to reach the goals established during the define stage.

With the inputs and outputs characterized and described, the discussion turns to examine the tools that can be used to evolve the design space using the QbD algorithm described earlier.

Tools for Developing the Design Space Using Quality by Design

Execution of the QbD loop during the design stage is a big effort requiring significant resources. Figure 12 summarizes some of the tools and approaches required to identify and resolve the issues of building effective control strategies. Good definition of the QTPP requirements (targets) should be defined by the medical and product development team working on the product. With these goals defined, the process development part of the define stage can begin.

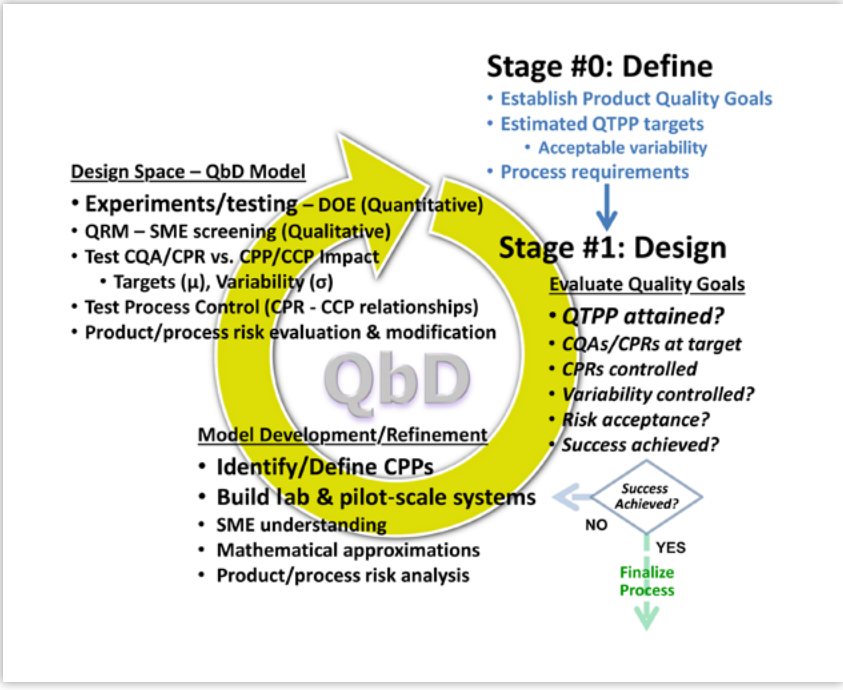


FIGURE 12. The design space is the process model used in the Stage #1 - Design step. The primary tools used to develop, qualify, and operate the model are shown. These tools are used to resolve future Stage 2 and Stage 3 issues, thus Quality is built into the process and product as early as possible in the lifecycle.

The initial task of Stage #1 is to begin assembling the process models required to build quality into the process unit operations. The models can include SME understanding, mathematical approximations, and lab and pilot-scale experimental systems. In addition, quality risk management (QRM) methods such as failure modes and effects analysis (FMEA) can be used to develop process understanding and assign priorities to best manage limited development resources. (This will be detailed in an upcoming BioProcessing Journal article.)

The models are then documented as an initial design space that are further developed and tested to put CQAs and CPRs at the required target values by manipulating the three types of input parameters defined above. The CQAs and CPRs are then tested against the goals or requirements to finalize the QbD cycle.

Some of the last QbD cycles should be directed at minimizing the variability of the CQAs and CPRs during operation. Efforts should also be undertaken to assure that all the CPPs are properly controlled with target values and variability consistent with the process's requirements. The design and features required for implementing all of the control strategies becomes an integral part of the design space definition.

Summary and Conclusion

In order to properly use Quality by Design during the design stage of the product's lifecycle, various process models are required. The process models are then systematically developed using many iterations of a QbD loop to provide a comprehensive understanding of the behavior and performance of the model's inputs and outputs. As the inputs (CPPs) and outputs (CQAs and CPRs) evolve and various elements of all the control strategies are added, the models combine to form the complete design space that describes both the process and the product being manufactured.

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