Review

Pharmaceutical BIOPROCESSING

Pharm. Bioprocess.
(2013) 1(1), 105–122

Quality by design for biopharmaceuticals: a historical review and guide for implementation

This article reviews the history of quality-by-design (QbD), how this concept has been applied to biopharmaceuticals, and what can be expected from implementation of QbD. Although QbD may lead to better design of products and manufacturing processes, and offers the potential for reduced regulatory compliance costs, it will likely increase development costs. Process developers will require additional skills and knowledge in the 'quality disciplines', which are not normally part of the training of those in biopharmaceutical process development. A model for implementing QbD in biopharmaceutical manufacture is proposed. The reader will gain an understanding of how QbD principles have been applied to the development of biopharmaceuticals, as well as learning of the potential drawbacks of applying QbD tools indiscriminately. Excellent examples of QbD applied to biopharmaceuticals in the literature will be highlighted and suggested as the direction for future development in this area.

Phillip Elliott*[1], Sam Billingham[1], Jingxiu Bi[2] & Hu Zhang[2]

[1]Hospira Adelaide, 8 Dalgleish Street, Thebarton, South Australia, 5031, Australia

[2]School of Chemical Engineering, The University of Adelaide, North Terrace, SA 5005, Australia

*Author for correspondence:
E-mail: phillip.elliott@hospira.com

A more modern approach to the development of pharmaceutical products and their subsequent manufacture has been advocated by the US FDA and the International Conference on Harmonization (ICH). This approach has been termed 'quality-by-design' (QbD) and 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*" [101]. There is much literature promoting the proposed benefits of QbD [1,2]; the benefits claimed for QbD include [3]:

- Better design of product;
- Fewer problems in manufacturing;
- A reduction in the number of supplements required for post-market changes;
- Understanding and mitigation of risk;
- Allowing for the implementation of new manufacturing technology without regulatory scrutiny;
- A reduction in overall cost of manufacturing;
- Less waste;
- Faster regulatory approval;
- Enabling continuous improvement;
- Providing a better understanding of processes and a better business model.

The key tools of QbD are incorporation of prior knowledge, the use of statistically designed experiments, risk analysis and knowledge management. The intent of QbD is to encourage pharmaceutical companies to develop sufficient understanding of their products and manufacturing processes; ensure that their processes are robust; and, demonstrate this enhanced understanding to the pharmaceutical regulatory agencies. Regulatory agencies have in turn suggested that demonstration of this 'enhanced knowledge' could allow for a more flexible regulatory approach [101]. For example, if a pharmaceutical product is

FUTURE SCIENCE

10.4155/PBP.13.6 ISSN 2048-9145

Key Terms

Risk analysis: Estimation of the risk associated with identified hazards. In a pharmaceutical context, this term is often used interchangeably with risk evaluation – the comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

Knowledge management: Systematic approach to collecting, analyzing, storing, and disseminating information related to products, processes and components.

Design space: Multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

Critical quality attributes: Physical, chemical, biological or microbiological property or characteristic of the product that should be within an appropriate limit, range or distribution to ensure the desired product quality.

Target product profile: Summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy, of a drug product is realized. Also referred to as the Quality Target Product Profile.

Drug product: Pharmaceutical product type that contains a drug substance, generally in association with excipients. Also referred to as the dosage form or finished product.

Drug substance: Active pharmaceutical agent which is subsequently formulated with excipients to produce the "drug product".

Design of experiment: Use of statistically designed experimental arrays to determine the effect of multiple variables on an experimental system that take into account experimental variation and are able to determine both the effects of each variable alone and the combined effect (interaction) of multiple variables.

approved for sale on the basis of a QbD application that includes a proposed design space, it may be possible to make changes to the manufacturing process after the product has been approved for sale, without the need to go through an expensive 'post-approval change process' with the pharmaceutical regulator. However, this level of regulatory flexibility is yet to be realised. It is hoped that the QbD approach will improve product quality and reduce regulatory compliance costs for pharmaceutical manufacturers. The concept promotes industry's understanding of the product and manufacturing process starting with product development, with the aim of building quality in from the start rather than trying to test quality of the product during manufacture.

Under the concept of QbD, when designing and developing a product, a company needs to define the desired product performance and identify critical quality attributes (CQAs). On the basis of this information, the company then designs the product formulation and manufacturing process to meet those product attributes. Ideally, it is hoped this will lead to understanding of the impact of raw material and equipment attributes and manufacturing process parameters on the CQAs, and identification and control of sources of variability. As a result of all of this knowledge, a company can continually monitor and update its manufacturing process to assure consistent product quality [4].

An important part of QbD is to identify the target product profile (TPP) of the intended drug product. The TPP is defined as a "*summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy, of a drug product is realized*" [101]. Once the TPP has been identified it is necessary to identify the CQAs of the intended product, with CQAs defined as "*a physical, chemical, biological or microbiological property or characteristic of the product that should be within an appropriate limit, range or distribution to ensure the desired product quality*" [101]. From the CQAs identified, the product design space can be determined, that is, specifications for in-process, drug substance and drug-product attributes [4]. The sum of acceptable variability in each of these attributes defines the overall product design space. The process design space can then be determined using risk analysis and design of experiment (DoE) techniques to determine the relationship of process parameter to the CQAs of the final product.

It should be noted that drug regulatory authorities generally base their decisions on three criteria – quality, efficacy and safety. However, they take no account of the actual or potential cost of the product to the company. Therefore, in addition to the need to be compliant with regulatory requirements, it is important for a company to examine the value for money it obtains from process development, acquisition of knowledge and QbD in general, and deploy these approaches in the most cost-effective manner [5]. A 2012 survey of industry participants found that approximately 20% of respondents thought that lack of cost–effectiveness was the biggest hindrance to adoption of QbD in biologics manufacturing, with a similar number citing fears of regulatory delays as the biggest hindrance [102].

In this article, the historical background of QbD is first reviewed, and then the implementation of QbD in biopharmaceutical manufacturing unit operations is examined. Finally, an approach to implementation of QbD is suggested and QbD is critiqued.

Historical background

In the 1990s, the FDA's focus shifted from regulating individual products to regulating the biotechnology industry as a whole [6]. The 1997 FDA Modernization Act established a new approach to reporting manufacturing changes, with the intent of minimizing the differences between applications for biologics and for drug approval, this act was later transposed into guidance documents [103–105]. The changes added more and more requirements for industry, resulting in increased review times. By the year 2000, the FDA realized that there were undesirable consequences of the regulatory review process [4] as manufacturers had become wary of implementing new technologies since it was unknown how regulators would perceive such innovation. This in turn led to higher costs for pharmaceutical manufacture due to the maintenance of wasteful and inefficient manufacturing processes. In many cases, the FDA attributed these high costs to low manufacturing efficiencies and the difficulty of implementing manufacturing changes [4]. In addition, the pharmaceutical industry

had been accused of under-performing in manufacturing innovation by the business community: "*Even as is it invents futuristic new drugs, its manufacturing techniques lag behind those of potato-chip and laundry-soap makers*" [7].

Due to concerns over the state of manufacturing, FDA oversight of firms increased. One result of this more stringent regulatory oversight was a dramatic increase in the number of manufacturing supplements to applications (these are approvals required from the FDA for a manufacturer to vary its process from that contained in the documentation already filed with the FDA). In 2007, the FDA received a total of 5000 supplements for new drug applications (NDAs) and biological license applications and abbreviated new drug applications (ANDAs) [4]. Considering that each of these supplements costs approximately $250,000 in direct costs alone [5], this increased regulatory oversight caused significant costs for the pharmaceutical industry (approximately $1.25 billion in 2007 alone based on these estimates).

cGMPs for the 21st century

A 2-year initiative, 'Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach' was launched by the FDA in August 2002. This initiative was intended to modernize the FDA's regulation of pharmaceutical quality for veterinary and human drugs and selected human biological products such as vaccines. The FDA acknowledged that the new strategy was required to alleviate concern among manufacturers that innovation in manufacturing and quality assurance would result in 'regulatory impasse' [106] – effectively, the cost of gaining approval for innovations became so high that innovation in manufacturing was almost completely discouraged. As part of this initiative, the pharmaceutical, as well as the chemistry, manufacturing and controls regulatory programs were evaluated [107].

The final report of this initiative was released in September 2004 [107]. In this report, the FDA stated that the guiding principles of its efforts to modernize the regulation of pharmaceutical manufacturing were:

- Risk-based orientation;
- Science-based policies and standards;
- Integrated quality systems orientation;
- International cooperation;
- Strong public health protection.

Importantly, in this report the FDA acknowledged that its primary focus remained the same – to minimize the risks to public health associated with pharmaceutical product manufacturing. The FDA stated, perhaps hopefully, that pharmaceutical manufacturing was evolving from an art to a science- and engineering-based activity. It was hoped that application of this enhanced science and engineering knowledge in regulatory decision making, establishment of specifications, and evaluation of manufacturing processes would improve the efficiency and effectiveness of both manufacturing and regulatory decision making. In this report the FDA identified a 'risk-based orientation' as one of the driving principles of the cGMP initiative with efficient risk management as the primary way to make the most effective use of FDA resources. A further guidance on process analytical technology (PAT) was released as part of the 'cGMPs for the 21st Century' initiative, which hoped to encourage the adoption of more modern and flexible manufacturing technology in the pharmaceutical industry [106].

Key Term

Process analytical technology: 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.

» ICH Q8: Pharmaceutical Development

Further codification of the QbD concept came with the release of the ICH Q8 guideline 'Pharmaceutical Development' [101] in November 2004. This guideline reached 'step 4' – recommendation for adoption by the regulatory agencies party to the ICH – in November 2005. A further annex to the guideline, intended to clarify the concepts in the original guideline, was released for public consultation in November 2007 and reached step 4 in November 2008 (the original guideline and the annex have subsequently been combined into a single document).

It is in the ICH Q8 annex that QbD is explicitly 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*" [101].

Two other important terms for discussing QbD were also defined in ICH Q8; Design Space and PAT. Design space is defined as "*the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality*". According to ICH Q8, working within the design space is not considered as a change as it has been demonstrated to have no impact on quality. Movement out of the design space would be considered to be a change and would normally initiate a regulatory post-approval change process. Based on this guideline, design space was to be proposed by the applicant and would be subject to regulatory assessment and approval. PAT was also defined in ICH Q8 as "*a system for designing,*

Key Term

Robustness: Ability of a process to reliably produce a product of the intended quality over a variety of operating conditions, at different scales or with different equipment.

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".

It should be emphasized that the ICH Q8 guideline provides guidance on the suggested contents of the Pharmaceutical Development section of the Common Technical Document. This section of regulatory submissions relates to the manufacture of the 'drug product' – this is a very specific term relating to the product that will actually be administered to the patient. This is in contrast to 'drug substance' or 'bulk material' which are the terms usually given to the active pharmaceutical agent that is subsequently formulated with excipients to produce the drug product [108]. This difference between drug product and drug substance is important when considering how and to what extent the original guidance was intended to apply QbD concepts and controls to pharmaceutical and biopharmaceutical manufacture. This original guideline did not relate to the manufacture of 'drug substance' – the active pharmaceutical ingredient (API) before it is formulated for administration to the patient. The complexity of unit operations for drug product is generally less than that for drug substance and it is appropriate that more control should be demonstrated for the drug product which will actually be administered to humans.

The ICH Q8 guideline indicated areas where the demonstration of greater understanding of pharmaceutical and manufacturing sciences could create a basis for flexible regulatory approaches. The guideline emphasized that more flexible regulatory approaches could be achieved if the applicant could demonstrate an 'enhanced knowledge' of product performance over a range of material attributes, manufacturing process options and process parameters. The methods suggested to achieve this enhanced knowledge were formal experimental designs or DoE studies, PAT and prior knowledge. Also suggested was the use of quality risk management principles to prioritize additional studies to collect such knowledge. ICH Q8 emphasized that it is the level of knowledge gained and not the volume of data generated that would lead to more favorable consideration by the regulatory bodies. A further suggestion was that applicant companies could assess the robustness of the manufacturing process, the ability of the process to reliably produce a product of the intended quality over a variety of operating conditions, at different scales or with different equipment, to support future manufacturing change and process improvement. The guideline suggests that changes during development should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space [101].

» ICH Q9: Quality Risk Management

ICH Q9 'Quality Risk Management' [109] was released at approximately the same time as ICH Q8 and ICH Q10, and needs to be considered as part of the overarching QbD guidance released by regulatory agencies. The purpose of ICH Q9 was to offer a systematic approach to quality risk management. It provided guidance on the principles and some of the tools of quality risk management for use by both regulators and industry in managing drug substances and drug products. Importantly, it noted that use of quality risk management can "*facilitate, but does not obviate, industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators*" [109].

Two important principles were outlined in this document for the use of Quality Risk Management:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient;
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

These are important caveats that should be remembered as risk assessment is a process that can easily be overused and lead to large amounts of unnecessary documentation.

In Annex 1 to ICH Q9 the following tools are suggested for risk management in the pharmaceutical industry:

- Flow charts;
- Check sheets;
- Process mapping;
- Cause and effect diagrams;
- Failure mode effects analysis (FMEA);
- Failure mode effects and criticality analysis;
- Fault tree analysis;
- Hazard analysis and critical control points;
- Hazard operability analysis;

- Preliminary hazard analysis;
- Risk ranking and filtering;
- Various statistical tools:
  - Acceptance control charts;
  - DoE;
  - Histograms;
  - Pareto charts;
  - Process capability analysis.

While acknowledging that the selection of quality risk management tools is dependent on specific facts and circumstances, Annex 2 to ICH Q9 suggested areas to which quality risk management tools could be applied by a pharmaceutical company, ranging across all operational areas from quality management to facilities maintenance and even final packaging and labeling. Of particular relevance to this review were the potential applications to the development phase of pharmaceuticals suggested by the ICH. Specifically, application of Quality Risk Management techniques was suggested to assess the critical attributes of raw materials, APIs, excipients and packaging materials, as well as to determine the critical process parameters for a manufacturing process. Other areas suggested in development were to assess the need for additional studies (e.g., bioequivalence and stability) in technology transfer and scale-up and to the reduction of variability in quality attributes.

» ICH Q10: Pharmaceutical Quality System

ICH Q10 reached 'step 4' in 2008 and described a model of an effective quality system for a pharmaceutical company. This model was intended to complement ICH Q8 and Q9 [110] and defines the ICH expectations for management responsibilities in a pharmaceutical company. The Pharmaceutical Quality System described had four key elements:

- A process performance and product quality monitoring system;
- A corrective action and preventive action system;
- A change management system;
- Management review of process performance and product quality.

Importantly, the guideline emphasized that these elements should be applied in a manner 'proportionate and appropriate' for each of the life cycle stages. That is, the same level of rigor is not appropriate for products in the development stage as in the commercial or discontinuation phases of a product's life cycle. It was the regulators' hope that adoption of ICH Q10 should "*facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities*". Knowledge Management and Quality Risk Management were cited as 'enablers' of this innovation and continual improvement. While movement within a registered design space would not require regulatory approval, the change should still be evaluated and documented by the company's change management system.

» ICH Q11: Development & Manufacture of Drug Substances

Dealing with the manufacture of Drug Substances, ICH Q11 'Development and Manufacture of Drug Substances (Chemical and Biotechnological/Biological entities)' was released for public consultation in May 2011 and reached step 4 in May 2012 [111]. Importantly for biological and biotechnological products this guideline stated that most of the CQAs of a biologically derived drug product are associated with the drug substance and, thus, are a direct result of the design of the drug substance or its manufacturing process. ICH Q11 reiterates the commitment to QbD principles in ICH Q8 and provides examples of how this process can be applied to drug substance manufacture. It then goes on to suggest where the data produced by QbD studies and risk assessments can be located in the Common Technical Document format.

While most of ICH Q11 is concerned with identifying what data should be presented in each section of the Common Technical Document, the appendices give some useful examples of the use of DoE experiments to establish the design space for different unit operations, both for small molecules (chemical entities) and biological products.

Of note is the fact that in these examples, when more than one CQA is affected by or dependent on a unit operation, the effective design space in which acceptable product is produced becomes smaller (**Figure 1**). This is likely to be a general result, especially so when more than one variable controls the output of a unit operation and the corresponding design space, therefore, has more than one dimension. For example, the design space shown in **Figure 1**, has two operating dimensions – conductivity and pH, but other unit operations may have additional operating dimensions such as linear flow velocity and product load that may also affect the CQAs of the product. In addition, the example given in ICH Q11 should be regarded as highly simplified due to the linear relationship shown between the variables and the product CQAs, which

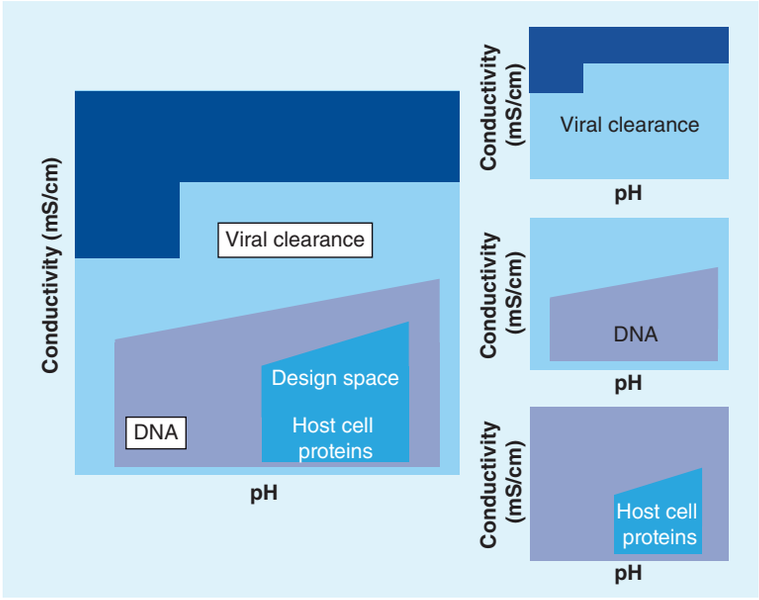

Figure 1. Design space for an anion-exchange chromatography unit operation, demonstrating the reduction in the design space when more than one critical quality attribute is dependent on a unit operation. Clear area in the small diagrams on the right illustrate the safe design space for each of the critical quality attributes individually. Clear area in the large diagram on the left indicates the safe design space for all critical quality attributes affected by the unit operation. Reproduced with permission from [111].

results in square or rectangular design spaces. In reality, these design spaces are generally complex curved surfaces for each CQA with statistical confidence intervals for each surface. Interpretation of such design spaces is more complex than for the example shown in ICH Q11.

Systematic review of QbD in manufacturing biological products

The European Federation of Pharmaceutical Industries and the European Medicines Agency have recognized that each product is unique – developing any product will require a 'bespoke' approach and, therefore, there is no standard blueprint for applying QbD [5]. Various methods of implementing QbD for entire processes have been suggested in the literature. One of the more useful and easier to follow methods is shown in **Figure 2** [4]. Initially, the TPP of the drug Product is identified. Once the TPP has been identified the relevant CQAs are identified and prioritized through the process of risk assessment. Based on the CQAs, the product design space is proposed – this is the sum of specifications for in-process, drug substance and drug product attributes. These proposed specifications are ideally based upon non-clinical studies, previous clinical experience with similar products, published literature and known process capability. Risk analysis is then performed to identify and prioritize parameters for process characterization. DoE studies are formulated to examine the process design space, the studies are then carried out and the results analyzed to determine the importance of the parameters examined. If necessary, the design space is then refined, based on the results of these initial studies. The control strategy for the unit operation is then defined through the process of risk assessment and based on the importance of the CQAs affected by the unit operation and the capability of the unit operation. As the biopharmaceutical product progresses toward regulatory filing, the unit operation is validated and routine monitoring of the process is carried out.

A more general introduction to using FMEA to classify and prioritize the parameters in a biopharmaceutical manufacturing process for further study has been presented in [8].

A QbD case study on the production of a model monoclonal antibody (A-mAb) has been developed by the International Society for Pharmaceutical Engineering [112]. This example includes sections on upstream (mammalian cell culture), downstream and drug product unit operations. It also includes sections on anticipated post-launch process changes – what is described as movement within the design space.

The case study noted that the overall control strategy for a manufacturing process is based on the design spaces of the individual unit operations – it is the sum of the individual control strategies that represent the overall control strategy.

The case study gives examples of constructing the TPP for the A-mAb molecule, followed by identification and risk assessment of quality attributes, leading to a rationale for selecting the CQAs for the case study. Three types of tools for assessing the criticality of quality attributes were used (risk ranking, preliminary hazard analysis and safety assessment decision tree) and examples given of how these tools are applied to the assessment of different quality attributes of the product (e.g., aggregation, glycosylation, deamidation, oxidation).

Various publications have reported the application of QbD techniques to many of the specific areas and unit operations of biopharmaceutical manufacture. The following section is a review of this literature as a reference for process developers to illustrate the different approaches that have been taken and the differences between individual areas and unit operations that make it necessary to modify the way in which QbD is implemented. In reviewing QbD literature and preparing DoE studies, careful attention should be paid to the definitions that will be used to classify each of the variables and the ranges within which each of the parameters can be controlled. A well-recognized scheme is to classify each operating vari-

able as either 'critical', 'key' or 'non-key' (Table 1) using the classification system produced by the Parenteral Drug Association [9]. The selection of variables to study and the definitions used to classify the criticality of those variables are pivotal in risk analysis and subsequent interpretation of DoE studies. This is because the criticality definitions include aspects of both how well the variable can be controlled within the defined range and how much of an effect that variable has on a CQA within that defined range. Many, if not all variables examined will affect the process to some degree, but the decision on whether to treat that variable as 'critical' depends on how it affects the final product administered to the patient and how easily the variable can be maintained within the desired range. Insufficient attention to the definitions used for variable classification can lead to haphazard overuse of both DoE and FMEA techniques.

» Cell culture

FMEA has been used to identify and prioritize the parameters for process characterization in the fermentation of *Pichia pastoris* [10] and *Escherichia coli* [11] and in mammalian cell culture producing mAb products in [12,13]. All of these examples start with the use of FMEA to classify and prioritize variables for experimentation, then move to DoE studies and development of the design space for the fermentation. The initial low resolution screening experiments using the selected variables (parameters) are followed by more targeted and thorough response-surface designs exploring the active variables determined in the screening design. A recent study has also used quality risk management procedures to choose between alternative cell culture technologies for the production of a mAb product [14].

In a fermentation process using *P. pastoris* [10] and methanol induction to express a soluble product, no critical parameters were identified in the fermentation as none of the variables examined affected final product quality within the experimental ranges examined and the process could be well controlled to remain within these ranges. The fermentation was, therefore , found to have a wide design space. Key parameters (those that affect process performance) identified in the study were temperature, pH and dissolved oxygen, all of which affected cell growth and titer. A 'worst-case' fermentation was then performed to verify the design space, in which

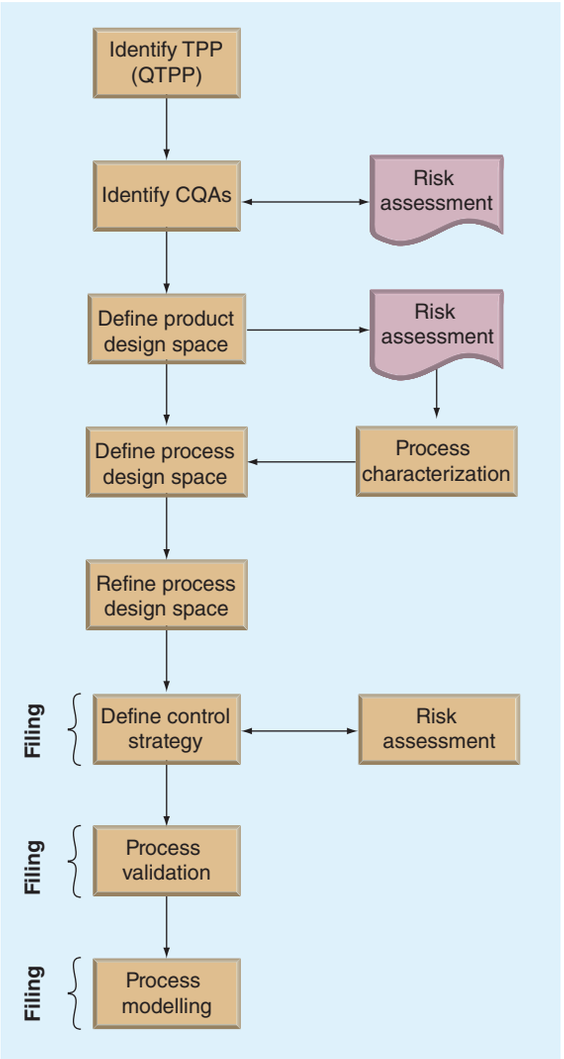

Figure 2. Suggested implementation plan for Quality by design.
CQA: Critical quality attribute; TPP: Target product profile; QTPP: Quality target product profile.
Reproduced with permission from [4].

Table 1. Parameter classification definitions.

Classification	Definition
Critical	An adjustable parameter (variable) of the process that should be maintained within a narrow range in order to not affect a product critical quality attribute
Key	An adjustable parameter (variable) of the process that, when maintained within a narrow range, ensures operational flexibility
Non-key	An adjustable parameter (variable) of the process that has been demonstrated to be well controlled within a wide range, although at extremes could have an impact on process performance

All input parameters outside this definition are non-critical.

all of the fermentation parameters were set to their most disadvantageous level in the design space. Although cell growth was affected, product yield and quality after purification were acceptable, verifying the robustness of the fermentation.

In comparison, for an *E. coli* fermentation [11] in which the product was deposited as insoluble inclusion bodies, temperature, feed rate, pH and dissolved oxygen (and interactions between these variables) were shown to affect product quality. A worst-case combination of parameters was then used to produce inclusion bodies. As the inclusion bodies produced in this worst-case could still be purified to produce acceptable product using the established downstream process, it was concluded that there were no critical operating parameters within the ranges tested as none of them affected the final product. Monte Carlo simulation was then applied to parameters and ranges selected for the design space to set acceptance criteria for process validation.

In mammalian cell culture expressing mAb products, the proportion of acidic variants has been found to be particularly sensitive to culture conditions [12,13]. Temperature, pH and initial viable cell density were confirmed to affect the glycosylation profile of the antibody product [12], however, as the downstream purification process was still able to produce an acceptable product from worst-case culture conditions, no critical variables were detected in the cell culture conditions. Initial DoE screening and follow-up response-surface experimentation was used to produce predictive models that allowed optimization of the cell culture process and could be used to monitor the success of scale-up and later commercial operations [12].

» Downstream processing

Chromatography

Examples of the use of FMEA applied to parameters of a chromatography unit operation are given in the appendix of ICH Q11 [111] and in the A-Mab case study [112].

Cecchini gives an example of the application of QbD techniques to the unit operations of cell harvest and product capture, protein A capture chromatography, hydrophobic interaction chromatography and anion exchange chromatography [15]. As with the approach taken in applying QbD to cell culture, all of these case studies follow the sequence of:

- Determining acceptable ranges for product quality attributes;
- Risk analysis to identify the most important unit operations to examine further to improve control of the overall process;
- Parameter screening – identification of key and critical parameters for modeling DoE through the use of Resolution III or IV screening DoE;
- Modeling DoE – Resolution V or response-surface designs to determine important interactions between variables and establish an empirical model for the important outputs;
- Scale-down model verification – comparison of modeling DoE to manufacturing scale runs.

A more mechanistic approach to ion-exchange chromatography has been taken in [16,17]. Both of these examples were built from the extensive theoretical knowledge of ion-exchange chromatography available in the literature to develop the design space for an ion-exchange unit operation and reduce the experimental and analytical requirements during process characterization. Kaltenbrunner *et al.* also compared the use of fractional factorial experiments to the theoretical model to validate the modeling approach [17]. Both approaches identified pH, ligand density and ionic strength at the start of the gradient as the dominant variables, providing assurance that the assumptions made to allow the modeling were valid. A similar treatment by Mollerup *et al.* was extended to provide a simulation of the resulting chromatogram generated from fundamental protein parameters and the ionic strength and pH of the running buffers [16]. This simulation was verified against small-scale and pilot-scale chromatograms and was able to confirm the root cause for a manufacturing problem that occurred at pilot scale.

Tangential flow filtration

QbD principles have been combined with a mechanistic understanding of tangential flow filtration (TFF) operations and applied to the development of a TFF unit operation [18]. Due to this approach, extensive DoE experiments were unnecessary, but more targeted experiments, guided by the mechanistic model, were able to quickly generate a robust method of operation and examine the economic implications of different operating modes. This work addressed issues of membrane selection, TFF design objectives, operating parameter design and operating mode design. It especially emphasized the need to determine the effect of temperature on the product, as the forces involved with TFF will generate heat – heat increases flux through the filtration membrane, but biopharmaceutical products can be especially sensitive to denaturation due to increased temperature. This article is important in that it begins from a mechanistic model of the technique of TFF, while also considering the applied aspects of the unit operation that will be important and unique to each

individual application. This approach is distinguished from more 'naive' DoE approaches that progress on a purely empirical basis and vary operating parameters without reference to mechanistic understanding of the unit operation.

This study does not consider the effect of electrostatic interactions during ultrafiltration of biopharmaceuticals since it deals primarily with a drug substance process. Electrostatic interactions should be taken into consideration in drug product TFF unit operations as protein biopharmaceuticals are highly purified and become the predominant charged species in solution. It is also important in the final drug product that exact concentrations of excipients are known and a target pH value is reached in the final solution. It has been shown that in the highly purified conditions of drug product TFF operations, electrostatic interactions between the biopharmaceuticals, the membrane and charged excipients can interact to significantly alter the final pH and excipient concentrations through the Donnan effect [19–22]. Special attention is required during the development of drug product TFF unit operations or any TFF unit operation in which the resultant buffer concentration and pH needs to be controlled within a narrowly specified range.

Viral & sterile filtration

The A-mAb case study provides a worked example of applying QbD principles to viral filtration and sterile filtration of drug product in which the combined use of risk assessment, prior knowledge from similar product experience and the development of a control strategy are illustrated [112]. For virus filtration two parameters, volumetric load and filtration pressure, were found to be important controls on virus removal and were classified as well-controlled critical process parameters. For sterile filtration five parameters were found to be critical, although all were easily controlled. Two of these parameters, pre-run flush volume with drug product and water for injection flush volume involved the preparation of the filter prior to use. The other three parameters identified as critical were the level of bioburden before filtration; flow rate per unit of membrane area; and, filter area.

» Drug product

Both the A-mAb case study and ICH Q8 provide examples of the use of QbD techniques to develop drug product unit operations such as lyophilization, sterile filtration, filling, stoppering and capping. While these unit operations are, by definition, high-risk due to their proximity to the patient, they are generally relatively simple and well characterized. The examples provided by the ICH guidelines have been rightfully criticized [23] as they provide examples of a one or two parameter design space only, whereas the design space for many unit operations can have many more than two parameters or dimensions. In designing these unit operations, care should be taken to ensure that the design space is as simple as possible to enable the resultant design space to be correspondingly simple. Compared with most of the API processing operations, linkage is not as complex in drug product processing primarily because the ranges are narrow and composition does not change as these are not purification steps. Therefore, there are not as many critical process parameters [24].

Martin-Moe *et al.* have focused on drug product unit operations for mABs as these are amenable to platform development and have a well-established clinical history [24]. This work used a risk ranking and filtering tool, rather than FMEA, to identify the CQAs affected by drug product unit operations. The output of this tool was used to determine which CQAs should be analyzed after each unit operation. A DoE study was then performed for formulation characterization with a risk-ranking tool used to support selection of ranges and the type of study proposed to establish the design space (multivariate vs univariate).

This work emphasized establishment of scale-down models to allow multivariate experimentation without excessive cost, and the importance of establishing the link between the large-scale process and the scale-down model. One alternative that has been presented is to use at-scale surrogate models that are not as costly as use of the actual product itself, but it is similarly important to establish the link between the surrogate model and the actual unit operation with product. For this reason, several companies now only produce biologics for Phase III trials in the same equipment as commercial product as they cannot otherwise assure comparability.

As discussed above, TFF unit operations at the drug product stage of processing suffer from the extra complexity introduced by the interaction of the charged biopharmaceutical, charged excipients and residual charge on the TFF membrane (Donnan effect) [19–22]. For this reason, particular attention should be given to the pKa's of the excipients, buffers and product and the extent of diafiltration when developing TFF unit operations for drug product.

» Raw materials

Lanan makes the very important point that raw materials have several distinguishing features from other aspects of biopharmaceutical manufacturing and this affects how they need to be handled in a QbD approach [25]. Unlike the operating parameters of a process, raw materials are not under the direct control of the biopharmaceutical manufacturer – they are the products of

others suppliers and their processes. In addition, complex or naturally derived raw materials can vary over much longer timescales than are required for process development. Therefore, even when efforts are made to use a variety of raw material lots or batches in process development, the total variation of the raw material may not be captured during process development due to the much shorter timeframe. Furthermore, for operating parameters and conditions, less attention is given to detecting variables once a process has been transferred to manufacturing. Raw materials may require the constant detection of variables even after the process has been transferred to manufacturing or commercial scale. This is because lot-to-lot, time-dependent changes to raw materials can occur during the manufacturing stage. QbD for raw materials may need to provide strategies to detect and manage changes in raw materials that may occur for the first time during commercial manufacturing. This is more in line with what has been described as a PAT or chemometric approach [26] .

Due to its complexity, special consideration needs to be given to cell culture media as a raw material. Cell culture media can contain more than 40 compounds [25]. Reactions can occur between these compounds, generating even more chemical complexity. The metabolism of the cells also alters these compounds, further increasing the complexity, making the whole system prone to variability from run-to-run. For some older mammalian cell-culture products, complex natural mixtures such as serum or plant hydrosylates are used in the media. These are complex mixtures and the analytical platforms required to characterize significant components of these mixtures are only now being developed [27]. Literature reports extensive use of many complex laboratory techniques (^{1}H-NMR, LC–MS, ICP–MS, LC–DAD) coupled with sophisticated statistical analysis (principal component analysis, partial least squares analysis, multivariate analysis, multilinear regression) to attempt to determine the root cause of variation in cell culture arising from these complex raw materials [25]. Some of these reports, even with such extensive efforts and sophisticated techniques, are not entirely successful in explaining the variation seen or completely determining root cause for out-of-trend results. For this reason it is probably prudent to avoid the use of complex or naturally derived components in cell culture as much as possible. Completely chemically defined media is likely to be more economical and reliable over the long term, even if it is not capable of producing the same yield of product in cell culture. It is fortunate that, while cell culture is often the most variable stage of biopharmaceutical production, it is also the most distant from the patient and variation at this stage is less likely to present risk to the patient. Experimental efforts to remove or replace naturally derived materials as far as possible, or explain, control and provide acceptance specifications for naturally occurring materials that must be retained in the process, are probably well spent and will contribute to overall control and QbD of cell culture. An examination of the history of quality improvement in the beer industry (the oldest biotechnology industry based on cell culture) shows the extensive efforts that have been exerted in controlling and reducing the variability of naturally derived raw materials in order to improve productivity and consistency [28]. Biopharmaceutical quality is already following the same pattern of development and the same approach to controlling raw materials is likely to be fruitful in improving the quality of the product.

Rathore and Low provide a useful scheme for classifying raw materials into critical, key and non-key categories [29,30]. They also provide a useful matrix or checklist of the categories of risk arising from raw materials and how these can be handled, although most of these are more traditional methods of handling raw material risk than being uniquely different for QbD. The second part of their paper gives examples of four different risk-assessment tools and demonstrates the application of FMEA to upstream and downstream materials along with an explanation of the logic for assigning different values for severity, occurrence and detection. In general, processes that are closer to the patient, especially drug product processes and the associated raw materials, should be considered higher risk than earlier processes. The risk-assessment team should begin with the most critical unit operations near the end of the process and work backwards through the process when assessing raw materials. At the end of the risk-assessment process the team should benchmark their scoring against the outcome of previous assessments for similar products and materials to ensure a consistent view of risk.

» Other

The use of a risk-assessment procedure to determine the CQAs of a mAb product has been described in [31]. This example illustrated the combined use of risk assessment procedures with prior knowledge and literature review. A recent study has tried to link experience in human clinical trials with mABs to physiochemical measures of the protein to further improve criticality determinations for this class of proteins [32].

The use of risk assessment as an adjunct to validation of an analytical assay is presented in [33]. The FDA has also indicated that it has accepted some NDA applications in which analytical methodologies are developed using a QbD approach and supplied a recommended approach for developing analytical tests in this manner [113].

Low pH viral inactivation, a common procedure for biopharmaceuticals expressed in mammalian cell culture, is developed from a QbD perspective in the A-mAb case study [112].

Implementation of QbD

The concept of QbD can be traced to Joseph Juran [34,35] and it is useful to return to some of his original works for the clarity with which they describe the concept of QbD. Juran's method for implementing QbD is shown in Figure 3 and was referred to by Juran as the 'quality planning roadmap' [36]. The virtue of this model is the ease with which it can be reduced to a step-by-step guide – Juran was quite conscious of the fact that deciding at which point to begin planning partly came down to a judgment call and decided on this series of steps to avoid repeated looping through the planning cycle [34]. The 'roadmap' has nine important steps: identifying customers; determining the needs of those customers; translating those needs into company language; developing a product that can respond to those needs; optimizing the product's features to meet both company needs and customer needs; developing a process that is capable of producing the product; optimizing the process; proving that the process can produce the product under operating conditions; and, transferring the process to operations [37]. Notably absent from the work of Juran is the use of risk assessment, as included in the ICH and FDA guidances. When considering use of the 'quality planning roadmap' in the biopharmaceutical industry it is useful to remember that some of the customers (indeed before marketing approval, the dominant customers) are the regulatory authorities involved, so many of the requirements that need to be sought from the customer should be sourced from the regulatory authorities and the relevant guidance and regulations. This is a very important point to remember in order to produce manufacturing processes and products that are compliant with regulation, while also producing a product with the required attributes.

Also pertinent is that Juran further subclassified customer needs into: stated needs, real needs, perceived needs, cultural needs and needs traceable to unintended use. This classification recognized the fact that the needs stated by customers are only a part of the whole needs – the customer has many other needs that are not consciously identified [34]. For example, regulatory agencies require that resin and membrane lifetime studies should be performed before a drug is approved for sale – this is a stated need. However, the real need is for a manufacturing process that performs consistently and reproducibly over the lifetime of the product and this real need should be considered for the process as a whole in addition to the stated needs of resin and membrane lifetime studies.

Developing a manufacturing process for a biopharmaceutical using QbD principles corresponds to the last 3 steps of the Quality Planning Roadmap (Figure 3) – 'Develop process features', 'Process designs', 'Establish process controls and transfer to operations'. In order to carry out these steps it is necessary for the previous 7 steps of the Quality Planning Roadmap to have been completed and documented for reference. These 7 prior steps are often not carried out by process development groups, they are generally the functions of different groups or senior management in the company so it is important to ensure the outputs of these previous steps are thoroughly communicated and recorded. It is also necessary for the process development group to remember that it has customers – the manufacturing or operations group to whom the process will be transferred for example – and the needs of these customers should be correctly identified.

A flowchart for implementing the 'Quality Planning Roadmap' in biopharmaceutical process development is

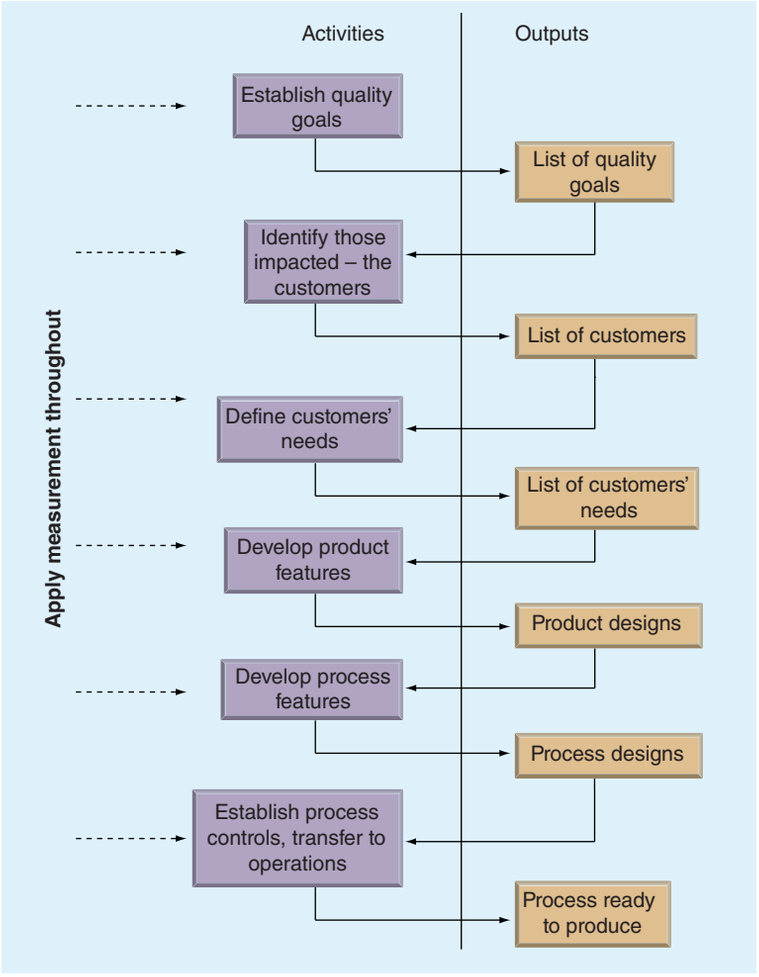

Figure 3. Juran's Quality Planning Roadmap.
Reproduced with permission from [36].

proposed by the authors and is shown in Figure 4. In broad outline the Roadmap consists of:

- Prioritizing unit operations for further study;
- Identifying the CQAs of the product;
- Identifying the CQAs affected by the highest priority unit operation;
- Prioritizing the CQAs to measure;
- Prioritizing operating variables for study;
- Designing and performing DoE studies;
- Recording the results.

This approach is intended to identify distinct outputs during QbD efforts, outputs that are necessary for communication and collaboration among the various groups inside a pharmaceutical company that must coordinate their efforts before, during and after product development. Before QbD can be implemented in a manufacturing process it is necessary to have a rudimentary initial process. Once this has been established, it is necessary to move backwards through the unit operations of the process, beginning with the last unit operation in the process train. It is important to progress in this manner as the output of each unit operation in a manufacturing process becomes the input for the next unit operation. Beginning at the start of the manufacturing process can lead to the initial unit operations being optimized, to the detriment of the subsequent unit operations and the overall manufacturing train. Progressing in this manner is also in itself a risk assessment or prioritization of work, with the level of risk of a unit operation generally thought to increase with proximity to the patient. This aligns with the fact that regulatory agencies will use risk assessments to determine which points in the process and which manufacturers and unit operations are most likely to cause risk to the final patient, and, therefore, require increased scrutiny [107,114,115]. The general rule of thumb of moving from the last unit operation back through to the initial unit operation could be replaced by a more formal risk assessment to identify areas of the process more likely to cause harm if they become out of control (developing a priority list of unit operations as shown in Figure 4). De-

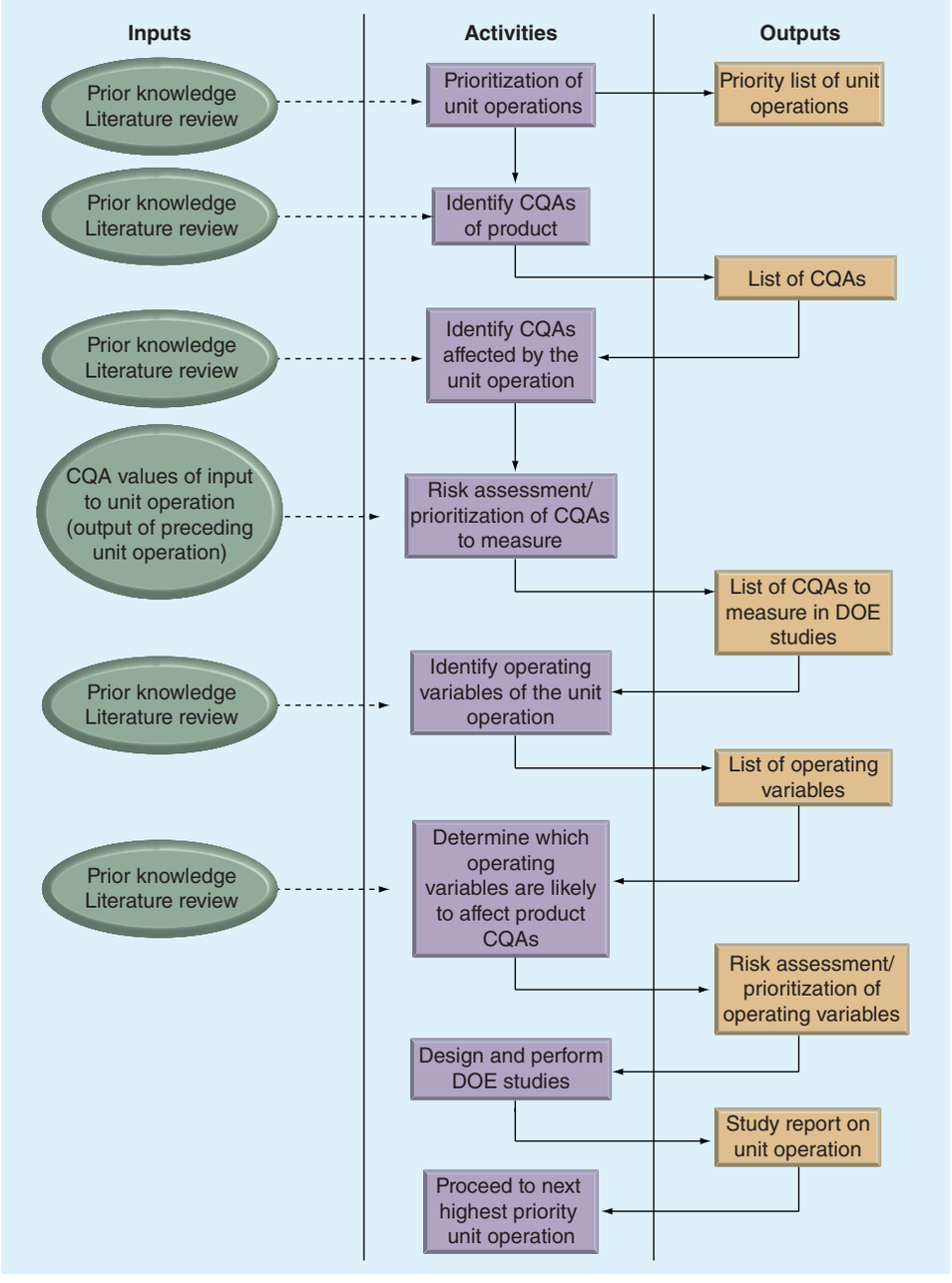

Figure 4. Suggested activities for implementing quality-by-design in downstream unit operations.
CQA: Critical quality attributes; DoE: Design of experiment.

termining the safe design space for the highest risk unit operations should be placed as the highest priority.

The next step in **Figure 4** is to identify the CQAs of the product, then go on to identify which CQAs are thought to be affected by the specific unit operation – this can be conducted using a combination of literature reviews, prior knowledge and risk assessment. Following this, the operating variables of the unit operation can be identified. A risk assessment can be performed on these variables – this should include a literature review and other prior knowledge. This risk assessment can then be used to determine which of these variables will affect, which may affect and which are unlikely to affect product CQAs. The next step in the process is to identify the values for the CQAs in the feedstock for the unit operation under consideration. This is effectively the output of the preceding unit operation. Having these values will allow determination of the effect of the unit operation on the CQAs. On the basis of the risk assessment and the values of the CQAs in the feedstock, the variables and outputs to measure in DoE studies can be determined and justified. Multivariate experimentation can then be carried out and the output levels of each of the CQAs compared with the inputs. This confirms whether each CQA is affected and whether the process variables chosen are robust within the ranges selected.

It may be useful to go through this exercise with a variety of processing technology alternatives for each unit operation in order to maintain flexibility for future improvements in technology. Demonstrating that acceptable CQAs are achieved over a multivariate range of parameters and a range of processing alternatives demonstrates the robustness of the manufacturing process. ICH Q8 identified that a more flexible regulatory approach could be achieved if the applicant could demonstrate an 'enhanced knowledge' of product performance over a range of 'material attributes, manufacturing process options and process parameters'. For unit operations that are intended to produce a specific CQA value or limit, it is useful to determine what maximum value can be used to challenge that unit operation, that is, if a chromatography step is designed to reduce deamidation variants in a product to a specification level it may be useful to challenge the unit operation in order to determine the maximum amount of deamidation variants that can be brought within the final specification. A study report on each unit operation should then be produced that identifies operating variables affecting the product and the safe operating ranges for those variables, along with identifying operating variables that did not affect the product in the unit operation [9]. Classifying in this manner is necessary to enable this information to be used in regulatory submissions that require disclosure of the critical steps and operating parameters in the manufacturing process.

After this exercise is completed the same exercise can be repeated with the next highest priority unit operation until the whole manufacturing process train is complete or the highest priority unit operations have been addressed.

Pitfalls of QbD

Risk management, statistical tools and knowledge management are all useful tools when implemented in the appropriate manner. However, these are all very broad concepts and, due to the large number of variables involved in any pharmaceutical manufacturing operation, the amount of experimentation and documentation required to thoroughly carry these out can become very large. In a recent approval application from Genentech, who has worked closely with the FDA on QbD, the chemistry, manufacturing and controls section was approximately 1500 pages in length due to the inclusion of all the backup data, risk assessments and justifications [116].

Similarly, DoE studies are a very effective tool and in many published papers QbD and DoE have almost become synonymous. However, the large number of variables that can be considered in a manufacturing process, especially a drug substance process, make the number of possible experimental runs very large. For example, the typical process chromatography unit operation can have 50–100 operating parameters that can affect its performance [38]. Examining all of these parameters would require a prohibitively large number of experimental runs. As a result of the increased experimentation and documentation required, a recent estimate has suggested that adoption of QbD approaches is likely to increase development costs by up to $1 million [23]. Due to the provenance of this estimate (from a report commissioned by the FDA and used to promote the QbD concept) it should be considered a conservative estimate likely to err on the low side. Evidence from the FDA that the generics industry, in which low development and production costs are competitive advantages, is much less keen on adoption of QbD would appear to support this (cited in [23]). Both the European Medicines Agency and FDA representatives have stated that they expect a more costly assessment process for QbD applications and the European Medicines Agency representatives also expect more difficult and costly inspections for QbD-based processes [23].

An additional concern is that the output of statistically designed experiments and the resulting design space can be a large and complex mathematical equation. Interpreting and applying this equation takes considerable mathematical and statistical knowledge

on behalf of both the pharmaceutical company and the regulatory agency reviewing the design space. A potential problem for companies is that the regulators, who would be required to approve the design space, may not have the mathematical knowledge required to correctly interpret the design space presented. At a recent conference of industry and representatives from various regulatory agencies, most attendees were unfamiliar with the concept of 'n-dimensional space' – a space having more than 1, 2 or 3 dimensions (n-dimensions). This concept is essential for interpreting complex design spaces as many reactions or processes can have more than two variables controlling the output. The European Medicines Agency representatives admitted that European Medicines Agency staff were 'challenged' in statistical knowledge and the FDA had not yet evaluated whether its staff had the requisite knowledge [23]. Elsewhere, representatives of the Canadian regulator Health Canada have stated that they are struggling to deal with QbD applications [5]. A survey of industry participants in 2012 indicated that many people in the pharmaceutical industry felt that the level of QbD understanding by FDA regulators was variable from individual to individual [116].

Not surprisingly, there appears to be widespread skepticism of the QbD concept, with a survey taken in 2008 showing that 58% of companies had QbD either in the 'ideas and vision' or 'not started' stage of implementation [39]. As the industry and regulators are not in a position to publish examples of QbD applications (due to confidentiality and intellectual property concerns) it has not been possible to fully allay these concerns. Up to mid-2010, a total of only five biological license applications and four post-approval supplements had been received for the biologics QbD trials [23].

Conclusion

QbD is not a unified system as such, but is more correctly described as an ethos that "*quality cannot be tested into products; it should be built in by design*" [115]. As such, it is difficult to prescribe a single solution for QbD – developing any product will require a bespoke approach and, therefore, there is no standard blueprint for applying QbD [5].

QbD is also an armory of techniques or tools that should be used for the development of good quality products and processes. These tools include: DoE, risk assessment, statistical quality control techniques (control charts) and mechanistic models, and understanding of processes and products.

In order to be able to implement QbD, biopharmaceutical companies should ensure they have these capabilities. Development staff and company scientists should be conversant with these tools and techniques. Joseph Juran, to whom the origins of QbD can be traced [35] stated that, "*Product development requires not only functional expertise; it also requires the use of a body of quality-related know-how*". He decried quality planning performed by 'amateurs' – people who have not been trained in the 'quality disciplines' – as one of the main causes of poor quality processes and products [34]. Training those who develop manufacturing processes (development scientists and engineers) in these quality disciplines is the only way to address this fundamental problem. Development scientists need a thorough understanding of these quality disciplines as their data and experiments form the basis of the processes and methods used during commercial manufacture [35].

It has been remarked that in order to develop the design space for a process, well-designed DoE experiments are required, but most process developers lack the statistical knowledge to effectively design these experiments [23]. For example, it is very easy with the use of DoE software to design a large, empirical study on a filtration or chromatography process. However, very detailed mechanistic models and understanding of these unit operations are already available in the chemical engineering literature. It is, therefore, not necessary to retreat to an entirely empirical level of understanding of these unit operations. Bringing the insights of mechanistic models to bear on specific applications in biopharmaceutical manufacturing requires very highly trained development scientists who can reduce the models to practice, and make the knowledge contained in the models available to technical staff who do not have the same level of scientific knowledge. Furthermore, development scientists need to be able to determine how to use the insights of such models on specific pieces of manufacturing equipment. Thus, a very important way for the quality of developmental products to be improved, and one of the hopes for the QbD initiative to be realized, is to ensure that development scientists are trained outside their original specialty disciplines in some (ideally all) of the tools of QbD. Similarly, as the QbD concept is being promoted by the pharmaceutical regulatory authorities it is imperative for those authorities to have staff that are familiar with and understand the limits and caveats of these tools. This is necessary in order for the authorities to be able to understand applications that present this information and be aware of when the information presented is insufficient.

Industry appears to have been restrained in the adoption of QbD, and considering the complexities involved and the apparent lack of understanding by the regulatory agencies on how to deal with applications of this type, such caution is understandable [23].

Hopes for greatly reduced costs of pharmaceuticals and reduced regulatory burden due to the QbD initiative should be limited. Much of the high cost of

pharmaceuticals is due to economic, political and regulatory factors [40]; which are unaffected by the science behind the original development work. None of these factors are likely to change due to the QbD or PAT initiatives; indeed, adoption of QbD approaches is almost certain to increase development costs [23].

The QbD concept is being used in the literature by development scientists to publish and share effective methods for process development and characterization. This is a welcome and useful development of the QbD concept and should help good practices become widely embraced throughout the industry and aid process development scientists in becoming cross-trained in quality disciplines. Some excellent examples in the literature have begun from mechanistic models of unit operations and have shown how these models can be used to develop robust and economical unit operations that are well characterized without having to assume only the empirical level of understanding implied in a naive DoE approach to the development of unit operations [16–18,38]. However, the way unit operations interact with a given product is less likely to be deducible from mechanistic models due to the complexity of biopharmaceutical products. How unit operations interact with the impurities in the product, which are in fact a wide variety of individual species (i.e., host cell protein, host cell DNA, viruses) is likely to resist mechanistic understanding as each individual host cell protein (for example) will have its own specific properties and clearance from the drug substance. For this reason, there will always be a level of 'empirical-only' knowledge required in the development of a biopharmaceutical and the need for traditional validation will remain.

Future perspective

The FDA has announced that it expects the pharmaceutical development (drug product) section of all ANDAs for small-molecule generic drugs to be in a QbD format from 1 January 2013 [117]. This change was achieved by updating the ANDA submission checklist to include QbD elements as requirements. This is likely to indicate that QbD will also become a requirement for biopharmaceuticals in the next 5–10 years. Close attention should, therefore, be paid to how QbD is applied to generics so that the lessons learned can be applied to more complex biopharmaceuticals in the future. Close attention should also be paid to how the QbD process has been implemented in the semicon-

Executive summary

cGMPs for the 21st Century
- The pharmaceutical cGMPs for the 21st Century initiative to improve innovation, risk-based orientation.
- ICH Q8: initial codification of QbD for Drug Product.
- Distinction between drug product and drug substance.
- ICH Q9: Quality Risk Management, quality related to patient safety, level of effort commensurate with risk.
- ICH Q10: Pharmaceutical Quality System, key elements expected of a quality system in a pharmaceutical company.
- ICH Q11: Development and Manufacture of Drug Substances, QbD for drug substance manufacture.
- Critical quality attributes of biological a direct result of drug substance process.

Systematic review of QbD in manufacturing biological products
- No standard blueprint for QbD.
- Empirical versus mechanistic approaches.
- QbD differences for raw materials and drug product unit operations.

Implementation of QbD
- Original QbD concept Juran – contrasts with FDA and International Conference on Harmonization concept.
- Juran's quality planning roadmap.
- Regulators as customers.
- A quality planning roadmap for biopharmaceuticals.

Pitfalls of QbD
- Size of QbD applications and increased costs of applications and assessments.
- Misapplication of design of experiment and risk assessment.
- Limited and variable expertise inside regulatory agencies.

Concluding remarks
- QbD as an ethos and an armoury of techniques.
- The requirement for training of process developers in quality disciplines.
- Superiority of mechanistic understanding over empirical.
- The continued need for empirical proof (validation) in a regulated industry.

Future perspective
- Possible mandating of QbD.
- Effects on innovation and smaller companies.

ductor and microelectronics industries over previous decades, as these industries have made significant improvements through the use of the quality disciplines and tools during development.

The majority of biopharmaceuticals under development are produced by small biotechnology companies who are under funding constraints and pressure to bring their products to market [5,23]. The increased funding requirements due to QbD may be most challenging to these companies, and the development of literature and industry guidance documents from regulators that can assist in addressing QbD requirements in a cost-effective manner will be necessary for these smaller companies to thrive in the QbD regulatory environment and, thus, maintain a vital element of new product development.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
■ of interest
■■ of considerable interest

1 Stevenson D, Cochrane T. Implementation of QbD part 1 – setting product specifications. *Reg. Rapporteur* 8(2), 3 (2011).

2 Stevenson D, Cochrane T. Implementation of QbD part 2 – organizational implications. *Reg. Rapporteur* 8(2), 3–16 (2011).

3 Kozlowski S, Swann P. Current and future issues in the manufacturing and development of monoclonal antibodies. *Adv. Drug Deliv. Rev.* 58(5–6), 707–722 (2006).

4 Rathore AS, Winkle H. Quality by design for biopharmaceuticals. *Nat. Biotechnol.* 27(1), 26–34 (2009).

5 Schmitt S. The roadmap to QbD. In: *Quality By Design: Putting Theory into Practice*. Schmitt S (Ed.). Davis Healthcare International Publishing, MD, USA, 31–54 (2011).

6 Kozlowski S. Protein therapeutics and the regulation of quality: a brief history from an OBP perspective: as the biotechnology industry has matured through various stages of growth, regulatory agencies have evolved in response to the need to define quality standards *Biopharm. International.* 20(10), 37–40 (2007).

■ **A useful history of the changes in regulation, from the US FDA's perspective.**

7 Abboud L, Hensley S. Drug manufacturing, out of date for years, gets a shot in the arm – US's FDA prods industry to adopt innovations, raise quality standards. *The Wall Street Journal Europe*, 03 September 2003.

8 Seely R, Haury J. Applications of failure modes effect analysis to biotechnology manufacturing processes. In: *Process Validation in Manufacturing of Biopharmaceuticals: Guidelines, Current Practices and Industrial Case Studies*. Rathore AS, Sofer G (Eds). CRC Press, Taylor and Francis Group, Boca Raton, FL, USA, 13–31 (2005).

9 Brandreth EJ, Bussineau C, Butler M *et al.* Validation of column-based chromatography processes for the purification of proteins. Technical report no. 14. *PDA J. Pharm. Sci. Technol.* 62(Suppl. 3) 2–36 (2008).

10 Harms J, Wang X, Kim T, Yang X, Rathore AS. Defining process design space for biotech products: case study of *Pichia pastoris* fermentation. *Biotechnol. Prog.* 24(3), 655–662 (2008).

11 van Hoek P, Harms J, Wang X, Rathore AS. Case study on definition of process design space for a microbial fermentation step. In: *Quality by Design for Biopharmaceuticals: Principles and Case studies*. Rathore AS, Mhatre R (Eds). John Wiley and Sons, Inc., NJ, USA, 85–108 (2009).

12 Abu-Absi SF, Yang L, Thompson P *et al.* Defining process design space for monoclonal antibody cell culture. *Biotechnol. Bioeng.* 106(6), 894–905 (2010).

13 Horvath B, Mun M, Laird MW. Characterization of a monoclonal antibody cell culture production process using a quality by design approach. *Mol. Biotechnol.* 45(3), 203–206 (2010).

14 Mila L, Valdes R, Tamayo A, Padilla S, Ferro W. Application of a risk analysis method to different technologies for producing a monoclonal antibody employed in hepatitis B vaccine manufacturing. *Biologicals* 40(2), 118–128 (2012).

15 Cecchini D. Applications of design space for biopharmaceutical purification processes. In: *Quality by Design for Biopharmaceuticals*. Rathore AS, Mhatre R (Eds). John Wiley and Sons, NJ, USA, 127–141 (2009).

16 Mollerup JM, Hansen TB, Kidal S, Staby A. Quality by design – thermodynamic modelling of chromatographic separation of proteins. *J. Chromatogr. A* 1177(2), 200–206 (2008).

■■ **A sophisticated approach to using the mechanistic models available for ion-exchange chromatography to achieve thorough characterization and effective control of a unit operation.**

17 Kaltenbrunner O, Giaverini O, Woehle D, Asenjo JA. Application of chromatographic theory for process characterization towards validation of an ion-exchange operation. *Biotechnol. Bioeng.* 98(1), 201–210 (2007).

■■ **A sophisticated, mechanistic approach to achieving quality by design for chromatography that demonstrates more understanding than simpler attempts that use standard design of experiment designs to build empirical models.**

18 Watler P, Rozembersky J. Application of QbD principles to tangential flow filtration operations. In: *Quality by Design for Biopharmaceuticals: Principles and Case Studies*. Rathore AS, Mhatre R (Eds). John Wiley & Sons, Inc., NJ, USA, 111–125 (2009).

■■ **Tangential flow filtration development taking into account both mechanistic understanding and the unique requirements of individual products.**

19 Bolton GR, Boesch AW, Basha J, Lacasse DP, Kelley BD, Acharya H. Effect of protein and solution properties on the Donnan effect during the ultrafiltration of proteins. *Biotechnol. Prog.* 27(1), 140–152 (2011).

20 Noordman T, Ketelaar T, Donkers F, Wesselingh J. Concentration and desalination of protein solutions by ultrafiltration. *Chem. Eng. Sci.* 57 (4) 693–703 (2002).

21 Rohani MM, Zydney AL. Role of electrostatic interactions during protein ultrafiltration. *Adv. Colloid Interface Sci.* 160(1–2), 40–48 (2010).

22 Stoner MR, Fischer N, Nixon L *et al.* Protein-solute interactions affect the outcome of ultrafiltration/diafiltration operations. *J. Pharm. Sci.* 93(9), 2332–2342 (2004).

▪ **Useful examples of the Donnan effect complicating Drug Product tangential flow filtration unit operations.**

23 Schmitt S. The regulatory framework. In: *Quality by design: Putting Theory Into Practice*. Schmitt, S (Ed.). Davis Healthcare International Publishing, MD, USA (2011).

24 Martin-Moe S, Lim FJ, Wong RL, Sreedhara A, Sundaram J, Sane SU. A new roadmap for biopharmaceutical drug product development: Integrating development, validation, and quality by design. *J. Pharm. Sci.* 100(8), 3031–3043 (2011).

25 Lanan M. QbD for Raw materials. In: *Quality by Design for Biopharmaceuticals.* Rathore AS, Mhatre R (Eds). John Wiley and Sons, NJ, USA, 193–208 (2009).

■■ **A very interesting discussion of the unique aspects of raw materials in quality-by-design (QbD) and the extraordinary efforts that must be used to fully characterize some of the complex raw materials used in cell culture.**

26 Pomerantsev A, Rodionova O. Process analytical technology: a critical view of the chemometricians. *J. Chemom.* 26(6), 299–310 (2012).

27 Luo Y, Chen G. Combined approach of NMR and chemometrics for screening peptones used in the cell culture medium for the production of a recombinant therapeutic protein. *Biotechnol. Bioeng.* 97(6), 1654–1659 (2007).

28 Curinova L, Dudek F. Quality management in nineteenth-century Czech beer and sugar PRODUCTION. In: *A History of Managing for Quality: The Evolution, Trends, and Future Directions of Managing for Quality*. Juran JM (Ed.). ASQC Quality Press, WI, USA, 657 (1995).

29 Rathore AS, Low D. Managing raw material in the QbD paradigm, part 1: understanding risks. *BioPharm. International* 23(11), 34–40 (2010).

30 Rathore AS, Low D. Managing raw materials in the QbD paradigm part 2: risk assessment and communication. *BioPharm. International* 23(12), 5 (2010).

31 Schenerman M, Axley M, Oliver C, Ram K, Wasserman G. Using a risk assessment process to determine criticality of product quality attributes. In: *Quality by Design for Biopharmaceuticals: Principles and Case Studies*. Rathore AS, Mhatre R (Eds). John Wiley and Sons, NJ, USA, 53–82 (2009).

32 Goetze AM, Schenauer MR, Flynn GC. Assessing monoclonal antibody product quality attribute criticality through clinical studies. *MAbs* 2(5), 500–507 (2010).

33 van Leeuwen JF, Nauta MJ, de Kaste D *et al.* Risk analysis by FMEA as an element of analytical validation. *J. Pharm. Biomed. Anal.* 50(5), 1085–1087 (2009).

34 Juran JM. Juran on quality by design: the new steps for planning quality into goods and services. Free Press, NY, USA (1992).

■■ **The original work on QbD that encompasses many more topics than design of experiment, risk assessment and target product profile.**

35 McConnell J, Nunnally BK, McGarvey B. The forgotten origins of Quality by Design. *J. Valid. Technol.* 16(3), 5 (2010).

■ **Traces the origins of QbD and calls for a re-emphasis on the control and elimination of variation as the foundation of good quality.**

36 Juran JM. Dr Juran and a call to action: the summit. *Measuring Business Excellence* 6(3), 4 (2002).

37 Bicheno J. *The Quality 60: a Guide for Service and Manufacturing*. PICSIE Books, Buckingham, UK (1998).

38 Kaltenbrunner O, McCue JT, Engel P, Mollerup JM, Rathore AS. Modeling of biopharmaceutical processes. Part 2: process chromatography unit operations. *BioPharm. International* 21(8), 28 (2008).

39 Neway J. How to make the business case for Quality by Design. *BioPharm International* 21(12), 42–50 (2008).

40 Friedman M. How to cure health care. Hoover Digest, 3 (2001).

» Websites

101 ICH. Pharmaceutical Development Q8(R2) 2009. www.ich.org/products/guidelines/quality/article/quality-guidelines.html

102 BioProcessTechnologyConsultants. Quality by Design: Just a Buzz Word? www.bptc.com/sites/default/files/biopulse_reports/qbd_results_2012–2005–15_final.pdf

103 USFDA. Guidance for Industry www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM124805.pdf

104 USFDA. Demonstration of comparability of human biological products, including therapeutic biotechnology-derived products. www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm

105 USFDA. Revised guidance for industry. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

106 USFDA. Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (2004). www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070305.pdf

107 USFDA. Pharmaceutical cGMPS for the 21st century - a risk-based approach: final report (2004). www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm137175.htm

108 ICH. Specifications: test procedures and acceptance criteria for biotechnological/biological products Q6B (1999). www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6B/Step4/Q6B_Guideline.pdf

109 ICH. Quality Risk Management Q9 (2005). www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf

110 ICH. Pharmaceutical Quality System Q10 (2008). www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf

111 ICH. Development and manufacture of drug substances (chemical entities and biotechnological/biological entities) Q11. www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_Step_4.pdf

112 CMCBiotechWorkingGroup. A-mAb: a case study in Bioprocess Development (2009). www.ispe.org/pqli/a-mab-case-study-version-2.1

113 Quality by Design approaches to analytical methods - FDA perspective (2011). www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM301056.pdf

114 USFDA. Pharmaceutical cGMPS for the 21st Century – a risk-based approach: second progress report and implementation plan (2003). www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm071836.htm

115 USFDA. Innovation and continuous improvement in pharmaceutical manufacturing pharmaceutical cGMPs for the 21st Century (2004). www.fda.gov/ohrms/dockets/ac/04/briefing/2004–4080b1_01_manufSciWP.pdf

116 Taylor N. FDA mixed messages create QbD confusion (2012). www.in-pharmatechnologist.com/Regulatory-Safety/FDA-mixed-messages-create-QbD-confusion-consultant

117 Is QbD a mandate for generics? FDA responds to confusion. pharma QbD (2012). www.pharmaqbd.com/qbd_mandate_generics_fda