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Quality by Design (QbD) for biotechnology-related pharmaceuticals

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Review

Workshop Report**Quality by Design (QbD) for biotechnology-related pharmaceuticals**

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Abbreviations: **CPP**, critical process parameters; **CQA**, critical quality attribute; **DoE**, design of experiments; **EMA**, European Medicines Agency; **FDA**, United States Food and Drug Administration, **ICH**, International Conference on Harmonization; **MAA**, marketing authorization application; **MVA**, multivariate analysis; **NIR**, near-infrared; **NME**, new molecular entities; **PAR**, proven acceptable range; **PAT**, process analytical technology; **QbD**, quality by design; **SPC**, statistical process control; **TPP**, target product profile

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Abstract

The following article is a report from a workshop on Quality-by-Design (QbD) held at the 7th European Symposium on Biochemical Engineering Science (7 September 2008, Faro, Portugal). The aim of the workshop was to provide an update on the present status of using QbD in biotechnology-related applications in the pharmaceutical industry. The report summarizes the essential parts of the presentations and covers the industrial, academic, and regulatory aspects of QbD. It concludes with recommendations for further work and development.

For Peer Review

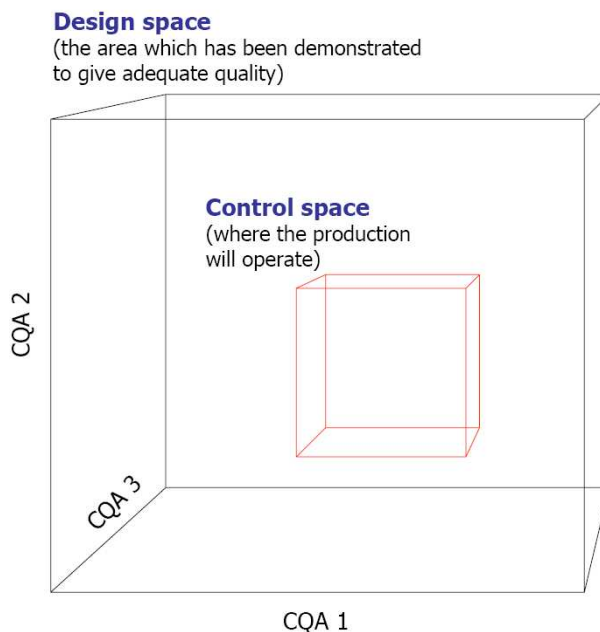
1 Introduction

The guiding principle of Quality-by-Design is that quality aspects must be integrated in the early stages of the production development, since good quality and production efficiency cannot be tested into products but must be built in by design.

Quality-by-Design (QbD) and the supporting enabling technology of Process Analytical Technology (PAT) unite modern scientific methodologies in modeling, sensor technology, analytical techniques and design. The concept is well-established in the academic community, and is already successfully pursued and applied in the pharmaceutical industry in a number of ways.

QbD was initiated in the pharmaceutical industry, the national regulatory authorities, and the academic world as a means of creating an early understanding of the design alternatives available during the development of a new drug. QbD should increase competitiveness where time constraints and increased customer quality demands are significant. These goals are explained in a variety of guideline documents from national bodies and worldwide industrial organizations, e.g. the ICH quality guidelines [1-4]. The United States' Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have adopted these guidelines in their regulatory framework for drug development and production [5].

The basics of QbD are illustrated in Figure 1. The *critical quality attributes* (CQAs) are the properties of the product that characterize its quality; they must be guaranteed in manufacture, otherwise the product must be discarded. Typical examples of such attributes are purity, stability, solubility, and product integrity, but ease of analysis is not uniform. The CQAs are a result of the product itself, but are also highly dependent on how the product is manufactured. This is controlled by the *critical process parameters* (CPPs). If the CPPs are properly selected and tuned, the right CQAs will be achieved. These must be maintained over time, a non-trivial task for biological processes given the natural variations in such systems and the time-dependent behavior of most batch operations.



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Figure 1. The design space and control space as defined in QbD

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The *design space* is the region where the parameter values can lie, while the *control space* defines the limits for their control. The design space is the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality. The control space is the subsection of the design space where the manufacturer chooses to operate. To do this successfully, a detailed and time-dependent understanding is essential. *This is where science can contribute significantly.* To accomplish this, we need reliable process analytical tools.

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PAT covers those methods that are useful 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. The term *analytical* is viewed broadly, and includes chemical, physical, microbiological, and mathematical aspects, as well as risk analysis. Typical PAT tools are those that enable scientific, risk-managed pharmaceutical development, manufacture, and quality assurance.

2 Adapting industrial production systems and procedures for QbD

QbD represents a holistic approach to the development of biotechnology-related pharmaceuticals. The novelty of the concept is evident in Table 1 and 2, which compares the traditional approach with the more advanced QbD approach.

Generally speaking, QbD encourages enhancement of the manufacturer's process understanding throughout the design space versus the traditional approach of filing commitments. When fully implemented, it could lead to more science-based validation and quality testing, and could also facilitate innovation and improvements in well-understood processes. These prospects may be attractive to the industry not only from a regulatory and quality perspective, but in the end also economically.

In the lifecycle of a product, QbD starts with the definition of the desired product properties. Then, during the process development phase, a multitude of input variables are linked systematically with output variables. Identification of the critical variables and parameters which have an impact on quality attributes (i.e. the CQAs) takes place at this stage. In the interest of reproducibility and process economics, those variables and parameters that have an impact on process robustness should also be identified and addressed thoroughly. At the same time, an appropriate process and product control strategy leading to a final drug product with pre-determined specifications should be developed.

As pointed out above, the final state of the product, the *target product profile* (TPP), must be defined before process development for clinical supplies can begin. Exhaustive physicochemical and bioanalytical characterization applying state-of-the-art methods in the field of protein characterization are vital, in order to create a comprehensive picture of the product and lower the risk of failures during the clinical development stage. Information on the composition of amino acid sequence variants, the secondary and tertiary structure, and post-translational modifications in detail; all this sets the stage for the design of expression systems, cell line screening, and process development. For example, the distribution of glycoforms of a given product may vary within mammalian cell populations, and can influence the biological properties dramatically. Careful

Table 1 Comparison of the traditional and QbD approaches

	Traditional Approach	QbD Approach
Broad Concept	Quality decisions 'divorced' from science and risk evaluation. Adherence to filing commitments.	Quality decisions and filing commitments based on Process Understanding and Risk Management. Design Space concept.
Quality	Post-manufacture sampling and quality testing. Process Validation.	Management of variability. Process control focused on critical attributes. Continuous Quality Verification.
Systems	Systems designed to inhibit changes & minimize business risks. Discourages improvement & innovation.	Changes managed within company's quality system. Real time batch release feasible. Higher reliance / trust / understanding on systems.
Regulatory	Compliance focus. Changes require prior approval, lengthy process, uncertain outcome.	Regulatory scrutiny adjusted to level of Process Understanding. Continuous improvement allowed within Design Space.

Source: Adapted from EFPIA, PAT Topic Group, 2005

Table 2 Important features of the QbD vision

Aspect	Starting point (Minimal approach)	Final QbD approach (Vision)
Development	<ul style="list-style-type: none"> mainly empirical one variable at a time 	<ul style="list-style-type: none"> systematic, relating input material attributes, process parameters to critical quality attributes multivariate experiments establishment of a design space
Manufacturing process	<ul style="list-style-type: none"> fixed focus on reproducibility validation based on full-scale batches 	<ul style="list-style-type: none"> adjustable within design space focus on control strategy and robustness lifecycle approach to validation, continuous process verification
Process controls	<ul style="list-style-type: none"> in-process tests primarily for go/no-go decisions off-line analysis 	<ul style="list-style-type: none"> PAT tools with feed forward and feedback loops use of statistical process control methods process ops tracked to support continual improvement efforts post-approval
Control strategy	<ul style="list-style-type: none"> Quality controlled primarily by intermediate and end product testing 	<ul style="list-style-type: none"> Quality ensured by a risk-based control strategy for a well understood product and process Quality controls shifted upstream; real time release or reduced end-product testing
Product specifications	<ul style="list-style-type: none"> Primary means of control Based on batch data available at time of registration 	<ul style="list-style-type: none"> Part of the overall quality control strategy Based on desired product performance with relevant supportive data
Lifecycle management	<ul style="list-style-type: none"> Reactive (problem solving, corrective action) 	<ul style="list-style-type: none"> Preventive action Continual improvement facilitated

adapted from draft Annex to ICH guideline Q8

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3 screening and analysis are required to select a productive clone which also delivers the
4 potential for a pre-defined target profile of glyco-variants. Together with receptor-target
5 binding data and cell-based activity assay data, sourced from actual measurements or the
6 public domain, the TPP can then be defined and targeted process development can begin.
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10 In the case of *innovative products*, including new molecular entities (NME), the QbD
11 definition process is of a more iterative nature, and is primarily based on the desired
12 biological properties. Factors such as available platforms for the production of the active
13 molecule, serum half-life, formulation, aggregation propensity, and immunogenicity must
14 be taken into consideration during development.
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18 From this work, the CQAs of the product can be defined. In particular, the elucidation of
19 structure-function relationships is a key aspect in the identification of CQAs, regardless
20 of whether innovative or biosimilar products are being developed. For the process and
21 production development, the most important question is that of which process parameters
22 impact CQAs, and to which degree and how controllably. A risk assessment may capture
23 the likelihood of occurrence and the potential effects of certain process parameters on
24 process robustness and, above all, on quality. A thorough risk assessment will therefore
25 be an integral part of this whole process.
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29 By definition, CPPs have an impact on quality attributes, and so must be controlled
30 tightly. Furthermore, the ICH Q8 guidelines propose a control strategy that ensures the
31 TPP specification is reached in a reproducible manner [1]. The control strategy will be
32 focused on (the critical) sources of variability, such as certain raw materials, but also the
33 inherent biological processes as a whole. The control strategy therefore encompasses all
34 input materials, unit operations, in-process testing (off-line, at-line, or on-line), and
35 finally the release tests. The level of process understanding strongly influences the design
36 of such a control strategy.
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40 During development, the analytical results recurrently contribute to adaptation and
41 optimization of the production system, leading to continuous improvement and
42 refinement of both the process and the product specifications. PAT-based development
43 tools, such as Design-of-Experiments (DoE), mathematical modeling, and multivariate
44 data analysis (MVA), when carefully applied during the characterization, will create a
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knowledge space which hosts the design space for the given process. When justified properly, movement within this design space would by definition not represent a change in the regulatory sense, and hence flexibility is increased.

Industrial applications of QbD

Biopharmaceutical companies may benefit substantially from applying QbD. One example is *Sandoz Biopharmaceuticals*, a leader in biosimilar product development, which has readily embraced many of the QbD elements. Based on the ICH guidelines, concept papers and development manuals have been established. Furthermore, PAT-related methods and tools such as DoE, MVA, and online monitoring tools have been adapted to in-house requirements.

MVA is currently being established on a manufacturing scale for the fermentation, isolation, and purification processes of one of Sandoz' commercial biotech products with the aim of learning more about process variability and thus finding out where to improve robustness. As a result, a QbD design space will be created which could justify regulatory flexibility. Important issues associated with this task are the inhomogeneities of signal traces due to spikes, and the generally much lower number of batches used for biopharmaceuticals in comparison to pharmaceutical products.

A number of spectroscopic tools are being developed in order to improve the control options for biological processes. One example is PTR mass spectrometry (Ionimed Analytik GmbH, Innsbruck, Austria) for assessment of patterns of volatile fermentation metabolites in real-time, thereby giving more insight into process performance and, ultimately, better process robustness.

For a company like Sandoz, QbD means a substantial investment in technologies, strategies, and skilled people. Implementation of QbD is, no doubt, a long-term undertaking and requires resources not only in technical development but also in production, quality, and regulatory support functions (see Table 2). Such investment should ultimately pay off by reducing production costs, by a more consistent quality, and by providing a more profound, science-based insight into biopharmaceutical processes.

Another company involved in QbD is *Boehringer Ingelheim Pharma* (BIP) and its Biopharmaceutical Division. BIP is a well-established contact manufacturer in the industrial biotechnology sector for over 25 years, and is known as a developer of highly innovative drugs. For BIP it is of utmost importance to keep up with the latest technologies, developments, and regulatory requirements in order to reduce both the cost of goods and the time to market. One of the prevailing aims is to develop production processes that reproducibly yield biopharmaceutical products with high product quality. Therefore, BIP is currently pursuing the implementation of QbD concepts, including PAT as a tool to improve process understanding, as proposed by the ICH Q8 guideline [1]. An example of the implementation of a PAT tool used at BIP is described below.

3 Enabling PAT tools

The main enabling PAT tools of QbD, when applied to biopharmaceutical processes, consist of (1) chemometrics computation methods and (2) bioanalytical methods and devices. Below the basics are described for applying chemometrics to QbD followed by a few examples of novel applications of bioanalysis.

Chemometrics for QbD

Design-of-Experiments (DoE) [6,7] has lately experienced a revival in the pharmaceutical industry due to initiatives towards QbD. The key factor in QbD is knowledge of the process, and in general mechanistic models are seen as the final aim and proof of complete understanding. DoE is, properly applied, a powerful tool both in the development of knowledge and in the determination of mechanistic models.

In short, one can say that to gain a higher level of knowledge, experiments are necessary. By planning the experiments according to DoE, the information gained from each experiment is maximized, thus increasing the prospects for solving the problems addressed. Using DoE as a basis for collecting information enables the calculation of predictive mathematical models that describe the relationships between changes in experimental conditions and the outcome of the experiments. Depending on the type of

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3 design applied, models with varying complexity — linear, interaction, or quadratic
4 effects — can be estimated. In addition, the mathematical model enables visualization of
5 the functions in the system.
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9 The importance of a properly performed problem formulation prior to DoE increases with
10 the complexity of the investigated system. In biological systems there are many factors to
11 consider, and in addition there are many sources of “noise” in the data due to
12 uncontrollable factors and biological variation. It is therefore very important to perform
13 the experiments in the DoE under as identical conditions as possible. This, in addition to
14 the costs, makes it cumbersome to perform DoE in large scale fermentation. On the other
15 hand, we have seen great success and gained much value and knowledge from applying
16 DoE in small scale fermentors run in parallel with a large-scale fermentor using the same
17 batch of nutrient feed.
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21 Once the DoE has been finalized, the data analysis remains. The length of the
22 fermentation processes means that sophisticated tools for data analysis are required, such
23 as MVA, which allows analysis of process evolution. With DoE and MVA in
24 combination a process can be characterized, the main drivers identified, and a deeper
25 understanding gained. Modeling of the process evolution allows real-time visualization of
26 the process status at any chosen time (Figure 2). The purpose of this could be monitoring
27 of how the process evolves compared to a defined “golden batch” or design space, early
28 detection of deviations, and identification of the cause of deviation. One value of these
29 models is that they generally detect drifts earlier than classical *statistical process control*
30 (SPC) charts, since multivariate models also identify deviations due to changes in
31 correlation pattern in the process.
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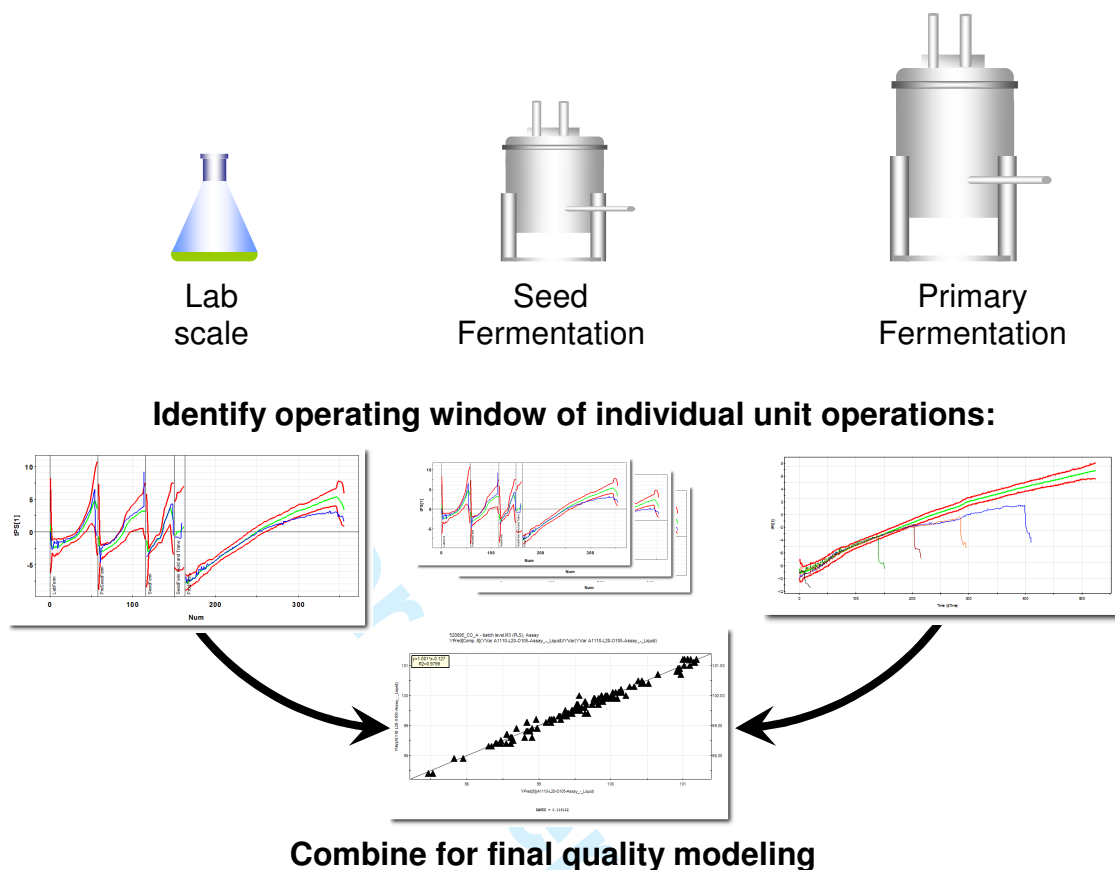


Figure 2. By combining DoE and multivariate data analysis techniques, a multi step process can be summarized in one overview model. This model links the entire history of a lot or batch to its final properties.

Continuous development of DoE and MVA tools is required as new data types emerge and the conditions for experimentation change; however, the tool box available today is usually sufficient for the current situation. The main limitations today are rather related to IT structure; that is, availability of data and data organization. There is also a need for improvement of in-line analytical instruments.

In order to turn DoE and multivariate techniques into commonly used tools, both in development and production, there is a need to simplify and adapt the toolbox for each specific application. The chemometrics supplier company Umetrics AB (Umeå, Sweden) provides highly qualified solutions for these techniques by creating user-friendly software without compromising the technical functionality and complexity. One successful

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3 approach is to integrate the techniques directly into instruments or equipment, allowing
4 the user to gain high value from the techniques without expert knowledge.
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8 9 **Bioprocess monitoring and control tools**

10 For animal cell culture processes in particular, PAT has been considered important for
11 improving efficiency and ensuring final product quality. To achieve these objectives, new
12 tools for on-line culture monitoring are necessary. While pH, temperature, dissolved
13 oxygen level, and cell density could be monitored today by *in-situ* probes, the
14 components of the cell culture supernatant are still quantified by time-consuming and
15 expensive off-line analyses. Spectroscopic methods, such as near infrared (NIR) and
16 Raman spectroscopy, have emerged for use in following nutrient consumption or
17 byproduct production in animal cell processes. Their advantages are various: non-
18 invasive and non-destructive techniques, no sampling, high frequency of spectra
19 acquisition, and large number of molecules potentially quantified. Their limitations
20 mainly concern analysis calibration, chemometric processing of the spectra, and previous
21 identification of strategic operating parameters and set-points. Papers reporting data on
22 this subject are focused on off-line [8-9], on-line [10], or *in situ* [11-12] NIR analyses,
23 mainly performed with suspension cell culture of CHO or Sf-9 cell lines. Ren and Arnold
24 [9] propose a comparison of multivariate calibration models for synthetic component
25 mixtures from NIR and Raman spectra. To our knowledge, no paper has reported data
26 with adherent cells cultivated in stirred reactors.
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42 Proper evaluation of NIR and Raman spectroscopy methods is highly desirable for cell
43 cultures. One example is adherent VERO cells cultivated in serum-free medium and on
44 microcarriers in spinner flasks and stirred bioreactors (CNRS, Université-Nancy, France).
45 The quantification of lactate and glucose was performed on culture media samples by off-
46 line measurements, and compared to data from reference enzymatic methods. NIR
47 spectroscopy data from chemometric analyses of spectra could be correlated to reference
48 results, contrary to the Raman results. Furthermore, no influence of microcarriers on
49 profile and quality of acquired NIR data was noticed, while Raman spectroscopy
50 presented an interesting sensitivity to cell physiological state. In a second experiment, *in*
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3 *situ* analyses were performed with a transfectance sterilizable NIR probe. Good
4 correlations were observed between NIR data and off-line reference results for glucose,
5 lactate, ammonium ions, and lactate dehydrogenase in culture medium. Thus,
6 spectroscopy methods represent a valuable asset for adherent animal cell cultures
7 analysis, and further developments would make these potential PAT tools for *in-situ*
8 monitoring and controlling animal cell processes.
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14 Another example of PAT is off-gas analysis, which can serve as an adequate tool to gain
15 comprehensive information about biopharmaceutical process conditions. Traditionally,
16 in-process control parameters have mainly included parameters such as viable cell count,
17 viability, product concentration, glucose concentration, glutamine concentration, lactate
18 concentration, ammonia concentration, osmolality, and pO_2 , among others. While these
19 are valuable for the monitoring of a biopharmaceutical fermentation process, it is likely
20 that additional physiological or metabolic data might reveal additional useful
21 information, thus deepening the understanding of the process. One such extra key
22 parameter could be the oxygen uptake rate (OUR). In mammalian cell cultivation, oxygen
23 is required to produce energy for both cell growth and energy maintenance. For example,
24 the aerobic degradation of carbohydrates (e.g. glucose) by glycolysis and the respiratory
25 chain reaction in the mitochondrion both depend on oxygen.
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36 Ideally, the conversion of 1 mol glucose and 6 mol O_2 yields 6 mol CO_2 , biomass and
37 energy. Thus, a strong relationship between glucose, oxygen consumption, and carbon
38 dioxide production is obvious with respect to the cell's energy metabolism.
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50 While traditional approaches to measure the OUR require a balance on the liquid phase
51 and further knowledge about the mass transfer coefficient k_La , which in turn is dependent
52 on many parameters such as media composition, gassing system, or bubble size [13], it is
53 now possible to apply a mass spectrometer as a sensitive and robust method to determine
54 the OUR *in situ* [14].
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60 At Boehringer Ingelheim, the OUR of different cell culture processes was studied by
using an off-gas quadrupole mass spectrometer. Online OUR data were presented
together with typical culture parameters, such as product concentration, from
representative fed-batch fermentations of different industrial relevant scales. It turned out

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3 that the application of the off-gas quadrupole mass spectrometer with online OUR data
4 revealed distinguishable levels of output parameters, while traditional in-process control
5 parameters were unable to provide proof of different process characteristics.
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9 Consequently, mass spectrometry offers a useful and precise PAT technique for gaining
10 further insight into the cell metabolism, as well as further opportunities to monitor
11 mammalian cell culture fermentations based on their respiratory activity.
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15 Several other methods useful for on-line or at-line monitoring of biopharmaceutical
16 processes have been presented and applied on a small scale [15]. Multi-wavelength
17 fluorimetry seems advantageous from several aspects – it is non-invasive and very
18 sensitive; and, due to its principle, it discriminates those compounds that fit the
19 excitation-emission combinations scanned for. However, it requires fluorescent properties
20 of the analytes probed for. Such analyte examples are found among the antibiotic
21 molecules and other small molecular metabolites [16].
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28 There is no doubt that analytical applications of genomic, proteomic, and transcriptomic
29 methods provide powerful tools to PAT. The omics tools have a unique possibility to
30 relate quality aspects to the CPP through a better understanding of systems biology
31 aspects in biopharmaceutical production [17]. So far, relatively few reports are available
32 on how identification and reduction of metabolic/physiological bottlenecks of the
33 biological systems can influence the quality of the production, and how this
34 understanding can subsequently be exploited with QbD methodology.
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44 **4 Regulatory aspects on the introduction of QbD for biopharmaceuticals**

45 *Regulatory considerations for biological molecules as pharmaceutical products*

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48 The viewpoints reported above have to be in perfect compliance with the long term
49 regulators' requirements on the biotechnology-related pharmaceuticals. Especially
50 biological processes and starting materials are more prone to variation, and the molecules
51 are often large and may be conjugated, for example as glycosylated and pegylated forms of
52 the product. These may be sensitive to oxidization, deamidation, and aggregation/
53 fragmentation. Changes may influence activity, but changes in for example glycosylation
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3 may in particular affect immunogenicity or clearance. No single method will allow for a
4 full characterization of the product, and subtle changes may even go unnoticed [18]. At the
5 same time, it is of key importance that the material produced on a commercial scale for the
6 market is representative in all important aspects of what has been shown to be efficacious
7 and safe during preclinical and clinical trials.
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12 The old paradigm for biopharmaceuticals — “one process - one product” — could be
13 interpreted as meaning that all changes to a production process require new clinical studies.
14 However, provided that comparability between the *pre-* and *post-change product* has been
15 shown, it is possible to introduce changes to the manufacture without additional clinical
16 studies [19].
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21 Alternative manufacturing processes (e.g. use of different clones expressing the same
22 protein or use of significantly different purification processes) are not allowed, but
23 flexibility within a given process is allowed if validated. The introduction of a properly
24 validated and documented QbD system and design space in the manufacture of biological
25 medicinal products therefore meets no formal obstacles. It should be noted that introduction
26 of QbD is optional, and the classical way with more emphasis on *end product testing* will
27 still be accepted, if appropriately documented [4].
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32 Many aspects interact in assuring full control of the product to be marketed. Control of
33 the raw and starting material (including cell banks) is particularly important for a
34 biological product, where the biological origin of the material can be expected to
35 introduce variability. *In-process controls* are performed to monitor whether the process is
36 behaving as expected. The process should be validated and shown to be robust and
37 reproducible. The production should be performed under Good Manufacturing Practices
38 (GMP), in order to ensure reliability, to assure adherence to approved production
39 methods, and to avoid the risk of contamination.
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44 As a final part of the quality control comes the testing of the active substance and the
45 finished medicinal product. These tests do not cover all aspects of the product, but a
46 number of relevant tests are picked to mirror the product characteristics under normal
47 production conditions. From these, and by taking risk assessment aspects into account,
48 the control strategy is formed. All parts need to be included, but the focus put on each of
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3 them may differ. When there is enhanced process understanding and appropriate
4 upstream testing and monitoring, testing of the finished stages may be reduced [1].
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8 In most cases the manufacturing process is changed during development, and as
9 mentioned above the applicant needs to show comparability throughout the whole
10 development in order to be able to refer to data gathered from earlier versions of the
11 process [19]. It is also expected that if a design space is established in the process, much
12 in-depth characterization will be required to verify that all combinations of CPP within
13 the design space will result in a comparable outcome, in terms of CQAs, to what has been
14 shown in clinical trials to be safe and efficacious.
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20 Difficulties may arise relating to the fact that only a few batches are used in clinical trials,
21 and hence these may not cover the full variability that can be expected in regular
22 production. An enhanced understanding of *structure-effect relationship* may therefore
23 simplify the establishment of models and allow the ruling out of non-significant
24 differences.
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29 For a deeper understanding of the processes, it is also important to evaluate potential
30 interactions between process parameters; by multivariate analysis or other methods [4].
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36 ***Aspects to consider in the introduction of QbD-based approaches***

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38 In the cases when similar molecules are produced, for example, monoclonal antibodies,
39 platform technologies are often used. However, prediction models have been shown to be
40 invalidated by small differences in, for example, buffers. To be fully able to extrapolate
41 from one product to another, it is important that the model is shown to also be fully
42 relevant to products for which the platform was not initially established.
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47 According to the control strategy concept, the sole fulfillment of a specification cannot be
48 considered a design space, since end testing is only one part of the strategy and the
49 specification will be process specific. Deviations from the accepted process may result in
50 impurities that will go unnoticed, as the specification is not designed to cover them.
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3 Furthermore, a combination of *proven acceptable ranges* (PARs) established by varying
4 one parameter at a time while keeping everything else locked will not be considered a
5 design space unless it has been shown that the parameters do not interact.
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9 When the QbD principles are introduced, the objective may not only include improved
10 quality, fewer rejections, and continuous production optimization, but also the possibility
11 of reduction in end product quality control testing or a reduction in filing of variations to
12 the Market Authorization. This will be considered acceptable, provided that at the end of
13 the manufacturing process there is an assurance of a product of predefined quality, linked
14 to what has been used to verify safety and efficacy [1]. As monitoring and quality
15 decisions will mainly be based on the parameters/attributes that are considered critical,
16 the arguments for classifying something as critical or non-critical need to be well-
17 explained to allow for an assessment of the control strategy.
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21 The new concept will have an impact on the work of regulators. The basis for approval
22 will not only be assessment of documentation submitted in the MAA, but also
23 documentation considered during inspections and assessment of the quality systems [3]
24 and risk assessment strategies [2] in place. This requires a close collaboration between
25 assessors and inspectors. To help with this and to keep up with the evolution of the field,
26 a specialized group, the EMEA PAT team, has been established. This group consists of
27 members from the Quality Working Party, the Biologicals Working Party, and the *ad hoc*
28 Inspectors' Working Party. It has regular contact with industry organizations and other
29 regulatory agencies to discuss common issues and provide expert knowledge for
30 applications dealing with QbD/PAT issues. Reports and question-and-answer sessions are
31 published on the EMEA website [20-22].
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46 As pointed out above, it is vital to make the link to the processes used to show safety and
47 efficacy in clinical trials. All flexibility introduced and all changes made to production
48 must result in a comparable product in all important aspects; relaxation of the level of
49 assurance in this respect compared to the current situation will not be accepted. A change
50 in the control strategy (e.g. less end product testing, increased flexibility within an
51 approved design space) is however allowed for, as long as equal or better quality can be
52 assured. Good transparency is of major importance for the successful introduction of
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3 QbD systems. The rationale for the proposals must be clearly described and supported by
4 documentation that describes the establishment of the proposed process in sufficient
5 detail. Raw data should not normally be submitted, but further information may be
6 requested if needed.
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11 While industry and regulators agree on the principles, interpretation differs between the
12 two and also within the industry and regulator groups themselves. QbD can be introduced
13 in many different ways, but it is important to agree on the basic principles and definitions
14 in order to avoid misunderstanding. The ICH Implementation working group will have an
15 important task in this respect.
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20 21 22 **4 Recommendations** 23

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25 The workshop resulted in a number of recommendations for how QbD in the area of
26 biotechnology-related pharmaceuticals can be improved and facilitated. The
27 recommendations are far from comprehensive, but are intended to highlight a few
28 pertinent issues. The following issues appear to be of particular urgency and relevance:
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33 i) *Better data management tools.* Biotechnology-related manufacturing generates a large
34 volume of data, which may be relevant or irrelevant to QbD analysis. This large volume,
35 along with the complex structure of the data, means that it is difficult to make an
36 overview, and so efficient analysis becomes unrealistic. Further development of
37 knowledge management systems [3], including more powerful data management software
38 tools, would be a valuable asset in mining for useful information.
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44 ii) *Retrieval of historical data.* When it comes to the use of historical data, one hurdle is
45 the availability of data. It is commonly *stored for storing* instead for *stored for use*,
46 meaning that it is difficult to retrieve and organize for multivariate modeling. This issue
47 has been recognized and addressed by many providers of data storage systems. It should
48 also be remembered that in most cases historical data does not contain enough variability
49 to yield all valuable information about a process. For existing processes, historical data is
50 usually the first step in a QbD investigation, but to fully explore the process a DoE is
51 required.
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iii) *Process understanding for control*. Ultimately, enhanced process understanding in combination with an appropriate control strategy could lead to real-time release. This long-term goal for biopharmaceuticals will certainly require better insight into what is currently often considered a black box. The following applied research topics could significantly improve our understanding of biological processes: (1) systems biology studies with omics tools to better understand metabolic networks and responses to stress and environmental conditions in general, (2) engineering of currently used hosts to eliminate bottlenecks, leading to a toolbox of optimized expression systems, (3) defined cultivation media, (4) understanding of structure-function relationships of the target molecule, and (5) improved downstream processing steps and purification concepts.

iv) *Criticality analysis and risk management*. The parameters in bioprocess engineering mostly differ from those for chemical drug substances. Consequently, they are of different origin and have a different impact on risk. Thus, a critical analysis of parameters, occurrence, and measurability would facilitate prioritization of specific needs.

v) *New real-time or just-in-time biospecific analyses and assays*. There is a need for further development of novel on-line/at-line monitoring tools for process development, and novel on-line/at-line monitoring tools for manufacturing. This should include rapid bio-specific analytical methods – such as glycoforms of proteins, other product variants, and side-product analysis in biotech process steps – which are not easily covered with typical systems biology analysis but call for more tailor-made assays. Biochemical engineering could contribute to further development of such methods on the basis of existing bio-recognition principles (e.g. biosensors, advanced multidimensional analyzers).

5 References

- [1] International conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH). Document ICH Q8 Pharmaceutical Development, 2005
- [2] International conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH). Document ICH Q9 Quality Risk Management, 2006
- [3] International conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH). Document ICH Q10 Note for Guidance on Pharmaceutical Quality System, 2008
- [4] International conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH). Document ICH Q8R Annex to Q8 Pharmaceutical Development. 2008
- [5] Federal Food and Drug Administration (USA) Centre for drug administration and research. Guidance for industry, process analytical technology, a framework for innovative pharmaceutical development, manufacture and quality assurance, FDA, 2004
- [6] Eriksson, L., Johansson, E., Kettaneh-Wold, N., *et al.* Design of Experiments: Principles and Applications. Umetrics AB, Umea, Sweden, 2008.
- [7] Mandenius, C.-F., Brundin, A., Review: Bioprocess optimization using DoE methodology, *Biotechnol. Prog.* 2008, in press
- [8] Arnold, S. A., Crowley, J., Woods, N., Harvey, L. M., McNeil, B., In-situ near infrared spectroscopy to monitor key analytes in mammalian cell cultivation, *Biotechnol. Bioeng.* 2003, 84, 13-19.
- [9] Ren, M., Arnold, M., Comparison of multivariate calibration models for glucose, urea, and lactate from near-infrared and Raman spectra. *Anal. Bioanal. Chem.* 2007, 387, 879-888.

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- [10] Rhiel, M. H., Cohen, M. B., Arnold, M. A., Murhammer, D. W., On-line monitoring of human prostate cancer cells in a perfusion rotating wall vessel by near-infrared spectroscopy. *Biotechnol. Bioeng.* 2004, 86, 852-861.
- [11] Riley, M. R., Crider, H. M., Nite, M. E., Garcia, R. A., Woo, J., Wegge, R. M., Simultaneous measurement of 19 components in serum-containing animal cell culture media by Fourier transform near-infrared spectroscopy. *Biotechnol. Prog.* 2001, 17, 376-378.
- [12] Riley, M. R., Rhiel, M., Zhou, X., Arnold, M. A. Murhammer, D. W., Simultaneous measurement of glucose and glutamine in insect cell culture media by near infrared spectroscopy. *Biotechnol. Bioeng.* 1997, 55, 11-15.
- [13] Schumpe, A., Quicker, G., Deckwer, W.D., Gas solubilities in microbial culture media. *Adv. Biochem. Eng.* 1982, 24, 1.
- [14] Oezemre, A., Heinzle, E., Measurement of oxygen uptake and carbon dioxide production rates of mammalian cells using membrane mass spectrometry. *Cytotechnology* 2001, 37, 153-162.
- [15] Eliasson Lantz, A., Jorgensen, P., Poulsen E., Lindemann C., Olsson, L., Determination of cell mass and polymyxin using multi-wavelength fluorescence. *J. Biotechnol.* 2006, 121, 544-554.
- [16] Clementschitsch, F., Bayer, K., Improvement of bioprocess monitoring, development of novel concepts. *Microbial Cell Factories* 2006, 5.
- [17] Duerrschmid, K., Reischer, H., Schmidt-Heck, W., Hrebicek, T., Guthke, R., Rizzi, A., Bayer, K., Monitoring of transcriptome and proteome profiles to investigate the cellular response of *E. coli* towards recombinant protein expression under defined chemostat conditions. *J. Biotechnol.* 2008, 135, 34-44.
- [18] International conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH). Document ICH Q6B Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, 2006
- [19] Mandate for the EMEA PAT team:
<http://www.emea.europa.eu/Inspections/docs/4832706en.pdf>

Manuscript for Biotechnology Journal (Wiley): Special issue from ESBES-7

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4 [20] Reflection paper on PAT related information in MA:
5 <http://www.emea.europa.eu/Inspections/docs/PATGuidance.pdf>
6
7
8 [21] International conference on harmonization of technical requirements for registration
9 of pharmaceuticals for human use (ICH). Document ICH Q5E Comparability of
10 Biotechnological/Biological Products, 2005
11
12
13 [22] Report from Workshop on Process Analytical Technologies for Biologicals, 15th
14 March 2007: <http://www.emea.europa.eu/pdfs/human/bwp/18537007en.pdf>
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For Peer Review

Table 1 Comparison of the traditional and QbD approaches

	Traditional Approach	QbD Approach
Broad Concept	Quality decisions 'divorced' from science and risk evaluation. Adherence to filing commitments.	Quality decisions and filing commitments based on Process Understanding and Risk Management. Design Space concept.
Quality	Post-manufacture sampling and quality testing. Process Validation.	Management of variability. Process control focused on critical attributes. Continuous Quality Verification.
Systems	Systems designed to inhibit changes & minimize business risks. Discourages improvement & innovation.	Changes managed within company's quality system. Real time batch release feasible. Higher reliance / trust / understanding on systems.
Regulatory	Compliance focus. Changes require prior approval, lengthy process, uncertain outcome.	Regulatory scrutiny adjusted to level of Process Understanding. Continuous improvement allowed within Design Space.

Source: Adapted from EFPIA, PAT Topic Group, 2005

Table 2 Important features of the QbD vision

Aspect	Starting point (Minimal approach)	Final QbD approach (Vision)
Development	<ul style="list-style-type: none"> mainly empirical one variable at a time 	<ul style="list-style-type: none"> systematic, relating input material attributes, process parameters to critical quality attributes multivariate experiments establishment of a design space
Manufacturing process	<ul style="list-style-type: none"> fixed focus on reproducibility validation based on full-scale batches 	<ul style="list-style-type: none"> adjustable within design space focus on control strategy and robustness lifecycle approach to validation, continuous process verification
Process controls	<ul style="list-style-type: none"> in-process tests primarily for go/no-go decisions off-line analysis 	<ul style="list-style-type: none"> PAT tools with feed forward and feedback loops use of statistical process control methods process ops tracked to support continual improvement efforts post-approval
Control strategy	<ul style="list-style-type: none"> Quality controlled primarily by intermediate and end product testing 	<ul style="list-style-type: none"> Quality ensured by a risk-based control strategy for a well understood product and process Quality controls shifted upstream; real time release or reduced end-product testing
Product specifications	<ul style="list-style-type: none"> Primary means of control Based on batch data available at time of registration 	<ul style="list-style-type: none"> Part of the overall quality control strategy Based on desired product performance with relevant supportive data
Lifecycle management	<ul style="list-style-type: none"> Reactive (problem solving, corrective action) 	<ul style="list-style-type: none"> Preventive action Continual improvement facilitated

adapted from draft Annex to ICH guideline Q8

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10 Figure 1.

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12 The design space and control space as defined in QbD
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17 Figure 2.

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19 By combining DoE and multivariate data analysis techniques, a multi step process can be
20 summarized in one overview model. This model links the entire history of a lot or batch
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Figure 1

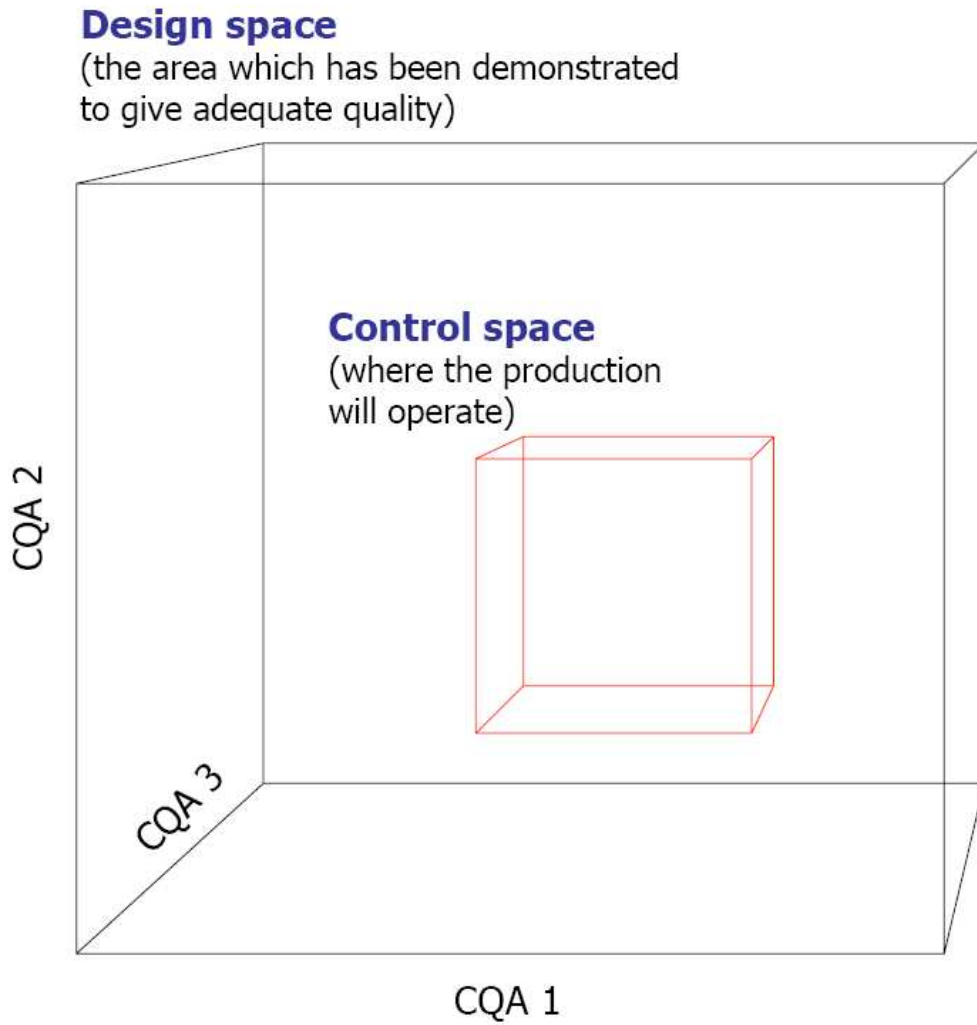


Figure 1. The design space and control space as defined in QbD

Figure 2

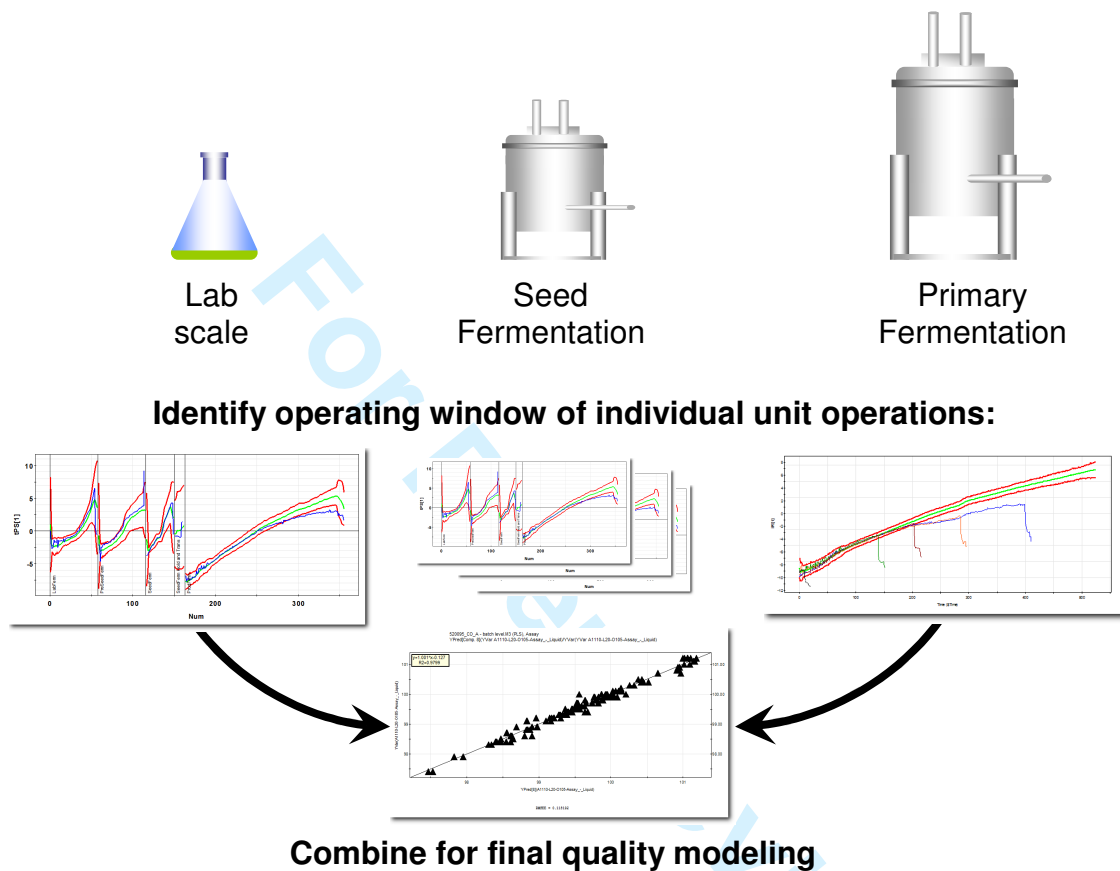
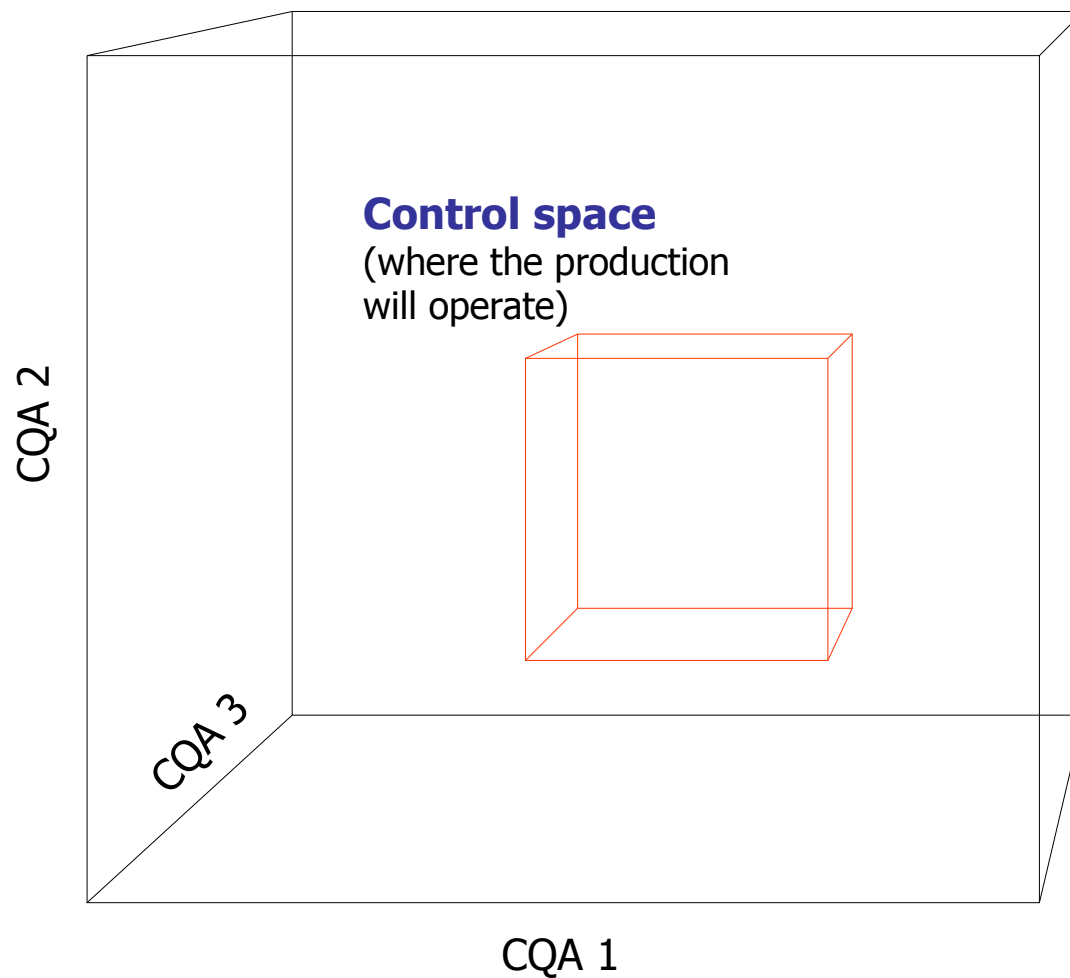


Figure 2. By combining DoE and multivariate data analysis techniques, a multi step process can be summarized in one overview model. This model links the entire history of a lot or batch to its final properties.

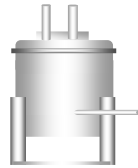
Design space

(the area which has been demonstrated to give adequate quality)

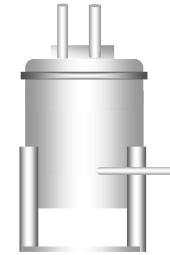




Lab scale

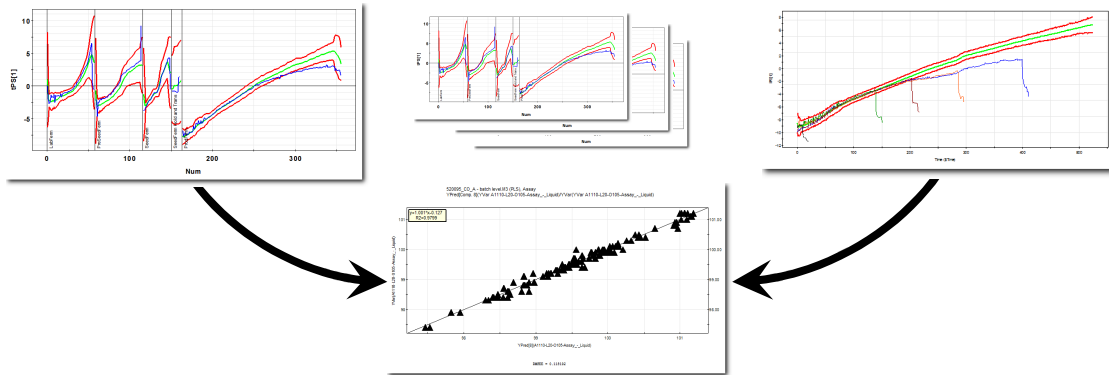


Seed Fermentation



Primary Fermentation

Identify operating window of individual unit operations:



Combine for final quality modeling

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