



Quality by Design (QbD) for biotechnology-related pharmaceuticals

Carl-Fredrik Mandenius

► To cite this version:

Carl-Fredrik Mandenius. Quality by Design (QbD) for biotechnology-related pharmaceuticals. Biotechnology Journal, 2009, 4 (6), pp.600-n/a. 10.1002/biot.200800333 . hal-00480831

HAL Id: hal-00480831

<https://hal.science/hal-00480831>

Submitted on 5 May 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



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

Journal:	<i>Biotechnology Journal</i>
Manuscript ID:	BIOT-2008-0333.R1
Wiley - Manuscript type:	Other contribution
Date Submitted by the Author:	30-Jan-2009
Complete List of Authors:	Mandenius, Carl-Fredrik; IFM, Biotechnology



Workshop Report

Quality by Design (QbD) for biotechnology-related pharmaceuticals

Carl-Fredrik Mandenius¹, Klaus Graumann², Torsten W. Schultz³, Andreas Premstaller²,
Ing-Marie Olsson⁴, Emma Petiot⁵, Christoph Clemens³, Mats Welin⁶

¹ Division of Biotechnology/IFM, Linköping University, Linköping, Sweden, ² Sandoz GmbH, Biopharmaceutical Operations, Kundl, Austria, ³ Boehringer Ingelheim Pharma GmbH & Co. KG, Germany, ⁴ Umetrics AB, Malmö, Sweden, ⁵ Laboratoire des Sciences du Génie Chimique/CNRS, Nancy-Université, Vandoeuvre-lès-Nancy, France, ⁶ Medical Products Agency, Uppsala, Sweden

Keywords: Design-of-Experiments; Design space; On-line monitoring and control; Biopharmaceuticals; Active pharmaceutical ingredients

Correspondence: Prof Carl-Fredrik Mandenius, IFM, Linköping University, S-581 83 Linköping, Sweden

E-mail: cfm@ifm.liu.se

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

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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

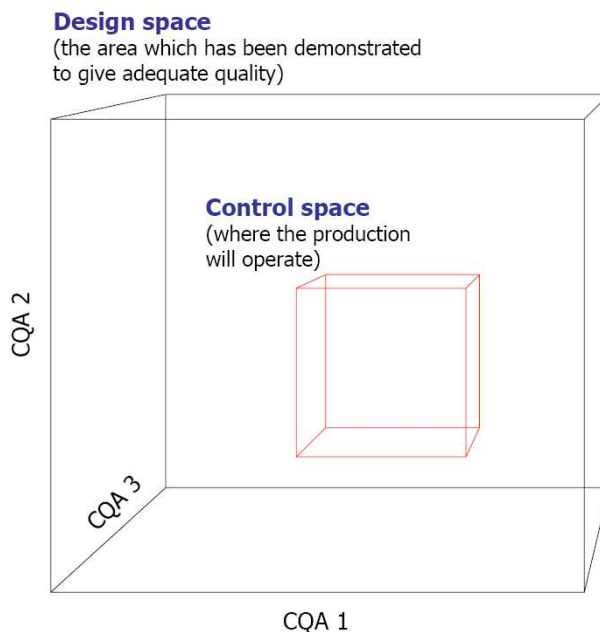


Figure 1. The design space and control space as defined in QbD

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.

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

screening and analysis are required to select a productive clone which also delivers the potential for a pre-defined target profile of glyco-variants. Together with receptor-target binding data and cell-based activity assay data, sourced from actual measurements or the public domain, the TPP can then be defined and targeted process development can begin.

In the case of *innovative products*, including new molecular entities (NME), the QbD definition process is of a more iterative nature, and is primarily based on the desired biological properties. Factors such as available platforms for the production of the active molecule, serum half-life, formulation, aggregation propensity, and immunogenicity must be taken into consideration during development.

From this work, the CQAs of the product can be defined. In particular, the elucidation of structure-function relationships is a key aspect in the identification of CQAs, regardless of whether innovative or biosimilar products are being developed. For the process and production development, the most important question is that of which process parameters impact CQAs, and to which degree and how controllably. A risk assessment may capture the likelihood of occurrence and the potential effects of certain process parameters on process robustness and, above all, on quality. A thorough risk assessment will therefore be an integral part of this whole process.

By definition, CPPs have an impact on quality attributes, and so must be controlled tightly. Furthermore, the ICH Q8 guidelines propose a control strategy that ensures the TPP specification is reached in a reproducible manner [1]. The control strategy will be focused on (the critical) sources of variability, such as certain raw materials, but also the inherent biological processes as a whole. The control strategy therefore encompasses all input materials, unit operations, in-process testing (off-line, at-line, or on-line), and finally the release tests. The level of process understanding strongly influences the design of such a control strategy.

During development, the analytical results recurrently contribute to adaptation and optimization of the production system, leading to continuous improvement and refinement of both the process and the product specifications. PAT-based development tools, such as Design-of-Experiments (DoE), mathematical modeling, and multivariate data analysis (MVA), when carefully applied during the characterization, will create a

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 contract 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

design applied, models with varying complexity — linear, interaction, or quadratic effects — can be estimated. In addition, the mathematical model enables visualization of the functions in the system.

The importance of a properly performed problem formulation prior to DoE increases with the complexity of the investigated system. In biological systems there are many factors to consider, and in addition there are many sources of “noise” in the data due to uncontrollable factors and biological variation. It is therefore very important to perform the experiments in the DoE under as identical conditions as possible. This, in addition to the costs, makes it cumbersome to perform DoE in large scale fermentation. On the other hand, we have seen great success and gained much value and knowledge from applying DoE in small scale fermentors run in parallel with a large-scale fermentor using the same batch of nutrient feed.

Once the DoE has been finalized, the data analysis remains. The length of the fermentation processes means that sophisticated tools for data analysis are required, such as MVA, which allows analysis of process evolution. With DoE and MVA in combination a process can be characterized, the main drivers identified, and a deeper understanding gained. Modeling of the process evolution allows real-time visualization of the process status at any chosen time (Figure 2). The purpose of this could be monitoring of how the process evolves compared to a defined “golden batch” or design space, early detection of deviations, and identification of the cause of deviation. One value of these models is that they generally detect drifts earlier than classical *statistical process control* (SPC) charts, since multivariate models also identify deviations due to changes in correlation pattern in the process.

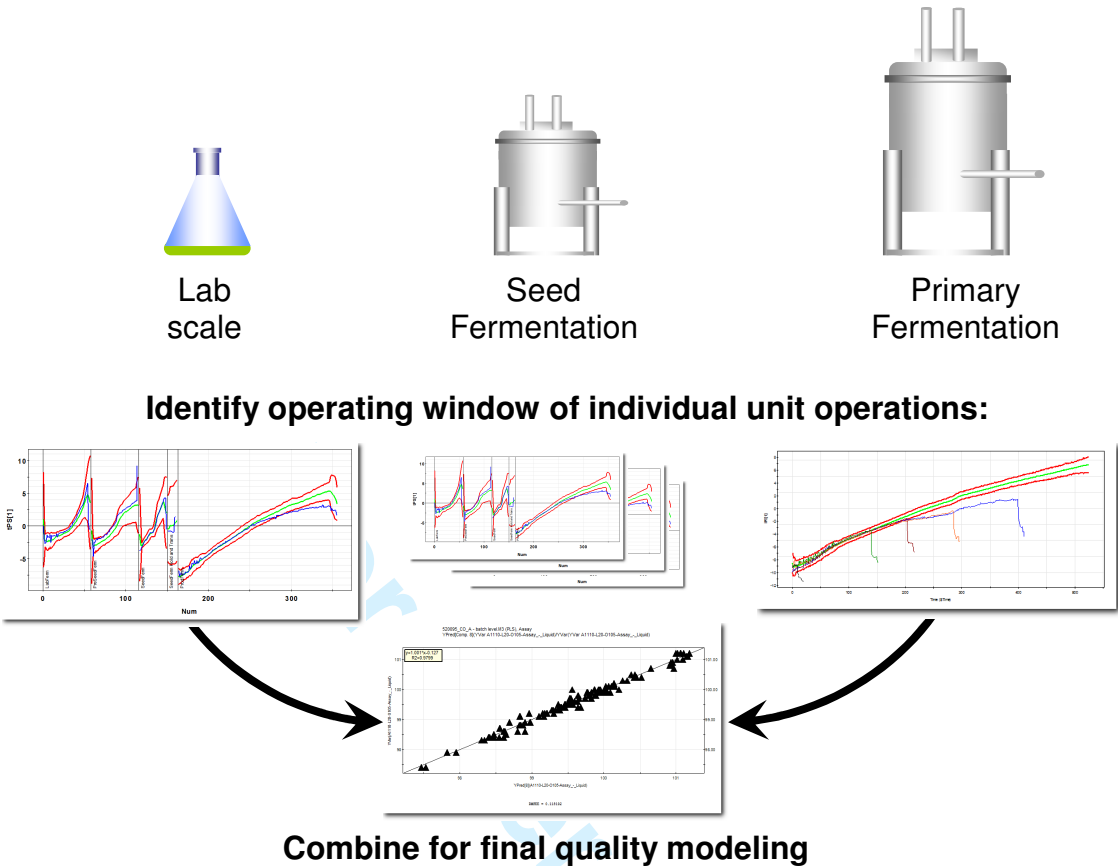


Figure 2. By combining DoE and multivariate data analysis techniques, a multi step process can be summarized in one overview model. This model links the entire history of a lot or batch to its final properties.

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

approach is to integrate the techniques directly into instruments or equipment, allowing the user to gain high value from the techniques without expert knowledge.

Bioprocess monitoring and control tools

For animal cell culture processes in particular, PAT has been considered important for improving efficiency and ensuring final product quality. To achieve these objectives, new tools for on-line culture monitoring are necessary. While pH, temperature, dissolved oxygen level, and cell density could be monitored today by *in-situ* probes, the components of the cell culture supernatant are still quantified by time-consuming and expensive off-line analyses. Spectroscopic methods, such as near infrared (NIR) and Raman spectroscopy, have emerged for use in following nutrient consumption or byproduct production in animal cell processes. Their advantages are various: non-invasive and non-destructive techniques, no sampling, high frequency of spectra acquisition, and large number of molecules potentially quantified. Their limitations mainly concern analysis calibration, chemometric processing of the spectra, and previous identification of strategic operating parameters and set-points. Papers reporting data on this subject are focused on off-line [8-9], on-line [10], or *in situ* [11-12] NIR analyses, mainly performed with suspension cell culture of CHO or Sf-9 cell lines. Ren and Arnold [9] propose a comparison of multivariate calibration models for synthetic component mixtures from NIR and Raman spectra. To our knowledge, no paper has reported data with adherent cells cultivated in stirred reactors.

Proper evaluation of NIR and Raman spectroscopy methods is highly desirable for cell cultures. One example is adherent VERO cells cultivated in serum-free medium and on microcarriers in spinner flasks and stirred bioreactors (CNRS, Université-Nancy, France). The quantification of lactate and glucose was performed on culture media samples by off-line measurements, and compared to data from reference enzymatic methods. NIR spectroscopy data from chemometric analyses of spectra could be correlated to reference results, contrary to the Raman results. Furthermore, no influence of microcarriers on profile and quality of acquired NIR data was noticed, while Raman spectroscopy presented an interesting sensitivity to cell physiological state. In a second experiment, *in*

situ analyses were performed with a transfectance sterilizable NIR probe. Good correlations were observed between NIR data and off-line reference results for glucose, lactate, ammonium ions, and lactate dehydrogenase in culture medium. Thus, spectroscopy methods represent a valuable asset for adherent animal cell cultures analysis, and further developments would make these potential PAT tools for *in-situ* monitoring and controlling animal cell processes.

Another example of PAT is off-gas analysis, which can serve as an adequate tool to gain comprehensive information about biopharmaceutical process conditions. Traditionally, in-process control parameters have mainly included parameters such as viable cell count, viability, product concentration, glucose concentration, glutamine concentration, lactate concentration, ammonia concentration, osmolality, and pO_2 , among others. While these are valuable for the monitoring of a biopharmaceutical fermentation process, it is likely that additional physiological or metabolic data might reveal additional useful information, thus deepening the understanding of the process. One such extra key parameter could be the oxygen uptake rate (OUR). In mammalian cell cultivation, oxygen is required to produce energy for both cell growth and energy maintenance. For example, the aerobic degradation of carbohydrates (e.g. glucose) by glycolysis and the respiratory chain reaction in the mitochondrion both depend on oxygen.

Ideally, the conversion of 1 mol glucose and 6 mol O_2 yields 6 mol CO_2 , biomass and energy. Thus, a strong relationship between glucose, oxygen consumption, and carbon dioxide production is obvious with respect to the cell's energy metabolism.

While traditional approaches to measure the OUR require a balance on the liquid phase and further knowledge about the mass transfer coefficient k_La , which in turn is dependent on many parameters such as media composition, gassing system, or bubble size [13], it is now possible to apply a mass spectrometer as a sensitive and robust method to determine the OUR *in situ* [14].

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

that the application of the off-gas quadrupole mass spectrometer with online OUR data revealed distinguishable levels of output parameters, while traditional in-process control parameters were unable to provide proof of different process characteristics.

Consequently, mass spectrometry offers a useful and precise PAT technique for gaining further insight into the cell metabolism, as well as further opportunities to monitor mammalian cell culture fermentations based on their respiratory activity.

Several other methods useful for on-line or at-line monitoring of biopharmaceutical processes have been presented and applied on a small scale [15]. Multi-wavelength fluorimetry seems advantageous from several aspects – it is non-invasive and very sensitive; and, due to its principle, it discriminates those compounds that fit the excitation-emission combinations scanned for. However, it requires fluorescent properties of the analytes probed for. Such analyte examples are found among the antibiotic molecules and other small molecular metabolites [16].

There is no doubt that analytical applications of genomic, proteomic, and transcriptomic methods provide powerful tools to PAT. The omics tools have a unique possibility to relate quality aspects to the CPP through a better understanding of systems biology aspects in biopharmaceutical production [17]. So far, relatively few reports are available on how identification and reduction of metabolic/physiological bottlenecks of the biological systems can influence the quality of the production, and how this understanding can subsequently be exploited with QbD methodology.

4 Regulatory aspects on the introduction of QbD for biopharmaceuticals

Regulatory considerations for biological molecules as pharmaceutical products

The viewpoints reported above have to be in perfect compliance with the long term regulators' requirements on the biotechnology-related pharmaceuticals. Especially biological processes and starting materials are more prone to variation, and the molecules are often large and may be conjugated, for example as glycosylated and pegylated forms of the product. These may be sensitive to oxidization, deamidation, and aggregation/fragmentation. Changes may influence activity, but changes in for example glycosylation

may in particular affect immunogenicity or clearance. No single method will allow for a full characterization of the product, and subtle changes may even go unnoticed [18]. At the same time, it is of key importance that the material produced on a commercial scale for the market is representative in all important aspects of what has been shown to be efficacious and safe during preclinical and clinical trials.

The old paradigm for biopharmaceuticals — “one process - one product” — could be interpreted as meaning that all changes to a production process require new clinical studies. However, provided that comparability between the *pre-* and *post-change product* has been shown, it is possible to introduce changes to the manufacture without additional clinical studies [19].

Alternative manufacturing processes (e.g. use of different clones expressing the same protein or use of significantly different purification processes) are not allowed, but flexibility within a given process is allowed if validated. The introduction of a properly validated and documented QbD system and design space in the manufacture of biological medicinal products therefore meets no formal obstacles. It should be noted that introduction of QbD is optional, and the classical way with more emphasis on *end product testing* will still be accepted, if appropriately documented [4].

Many aspects interact in assuring full control of the product to be marketed. Control of the raw and starting material (including cell banks) is particularly important for a biological product, where the biological origin of the material can be expected to introduce variability. *In-process controls* are performed to monitor whether the process is behaving as expected. The process should be validated and shown to be robust and reproducible. The production should be performed under Good Manufacturing Practices (GMP), in order to ensure reliability, to assure adherence to approved production methods, and to avoid the risk of contamination.

As a final part of the quality control comes the testing of the active substance and the finished medicinal product. These tests do not cover all aspects of the product, but a number of relevant tests are picked to mirror the product characteristics under normal production conditions. From these, and by taking risk assessment aspects into account, the control strategy is formed. All parts need to be included, but the focus put on each of

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

them may differ. When there is enhanced process understanding and appropriate upstream testing and monitoring, testing of the finished stages may be reduced [1].

In most cases the manufacturing process is changed during development, and as mentioned above the applicant needs to show comparability throughout the whole development in order to be able to refer to data gathered from earlier versions of the process [19]. It is also expected that if a design space is established in the process, much in-depth characterization will be required to verify that all combinations of CPP within the design space will result in a comparable outcome, in terms of CQAs, to what has been shown in clinical trials to be safe and efficacious.

Difficulties may arise relating to the fact that only a few batches are used in clinical trials, and hence these may not cover the full variability that can be expected in regular production. An enhanced understanding of *structure-effect relationship* may therefore simplify the establishment of models and allow the ruling out of non-significant differences.

For a deeper understanding of the processes, it is also important to evaluate potential interactions between process parameters; by multivariate analysis or other methods [4].

Aspects to consider in the introduction of QbD-based approaches

In the cases when similar molecules are produced, for example, monoclonal antibodies, platform technologies are often used. However, prediction models have been shown to be invalidated by small differences in, for example, buffers. To be fully able to extrapolate from one product to another, it is important that the model is shown to also be fully relevant to products for which the platform was not initially established.

According to the control strategy concept, the sole fulfillment of a specification cannot be considered a design space, since end testing is only one part of the strategy and the specification will be process specific. Deviations from the accepted process may result in impurities that will go unnoticed, as the specification is not designed to cover them.

Furthermore, a combination of *proven acceptable ranges* (PARs) established by varying one parameter at a time while keeping everything else locked will not be considered a design space unless it has been shown that the parameters do not interact.

When the QbD principles are introduced, the objective may not only include improved quality, fewer rejections, and continuous production optimization, but also the possibility of reduction in end product quality control testing or a reduction in filing of variations to the Market Authorization. This will be considered acceptable, provided that at the end of the manufacturing process there is an assurance of a product of predefined quality, linked to what has been used to verify safety and efficacy [1]. As monitoring and quality decisions will mainly be based on the parameters/attributes that are considered critical, the arguments for classifying something as critical or non-critical need to be well-explained to allow for an assessment of the control strategy.

The new concept will have an impact on the work of regulators. The basis for approval will not only be assessment of documentation submitted in the MAA, but also documentation considered during inspections and assessment of the quality systems [3] and risk assessment strategies [2] in place. This requires a close collaboration between assessors and inspectors. To help with this and to keep up with the evolution of the field, a specialized group, the EMEA PAT team, has been established. This group consists of members from the Quality Working Party, the Biologicals Working Party, and the *ad hoc* Inspectors' Working Party. It has regular contact with industry organizations and other regulatory agencies to discuss common issues and provide expert knowledge for applications dealing with QbD/PAT issues. Reports and question-and-answer sessions are published on the EMEA website [20-22].

As pointed out above, it is vital to make the link to the processes used to show safety and efficacy in clinical trials. All flexibility introduced and all changes made to production must result in a comparable product in all important aspects; relaxation of the level of assurance in this respect compared to the current situation will not be accepted. A change in the control strategy (e.g. less end product testing, increased flexibility within an approved design space) is however allowed for, as long as equal or better quality can be assured. Good transparency is of major importance for the successful introduction of

QbD systems. The rationale for the proposals must be clearly described and supported by documentation that describes the establishment of the proposed process in sufficient detail. Raw data should not normally be submitted, but further information may be requested if needed.

While industry and regulators agree on the principles, interpretation differs between the two and also within the industry and regulator groups themselves. QbD can be introduced in many different ways, but it is important to agree on the basic principles and definitions in order to avoid misunderstanding. The ICH Implementation working group will have an important task in this respect.

4 Recommendations

The workshop resulted in a number of recommendations for how QbD in the area of biotechnology-related pharmaceuticals can be improved and facilitated. The recommendations are far from comprehensive, but are intended to highlight a few pertinent issues. The following issues appear to be of particular urgency and relevance:

i) *Better data management tools.* Biotechnology-related manufacturing generates a large volume of data, which may be relevant or irrelevant to QbD analysis. This large volume, along with the complex structure of the data, means that it is difficult to make an overview, and so efficient analysis becomes unrealistic. Further development of knowledge management systems [3], including more powerful data management software tools, would be a valuable asset in mining for useful information.

ii) *Retrieval of historical data.* When it comes to the use of historical data, one hurdle is the availability of data. It is commonly *stored for storing* instead for *stored for use*, meaning that it is difficult to retrieve and organize for multivariate modeling. This issue has been recognized and addressed by many providers of data storage systems. It should also be remembered that in most cases historical data does not contain enough variability to yield all valuable information about a process. For existing processes, historical data is usually the first step in a QbD investigation, but to fully explore the process a DoE is required.

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.

- [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] Duerschmid, 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

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

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 empiricalone variable at a time	<ul style="list-style-type: none">systematic, relating input material attributes, process parameters to critical quality attributesmultivariate experimentsestablishment of a design space
Manufacturing process	<ul style="list-style-type: none">fixedfocus on reproducibilityvalidation based on full-scale batches	<ul style="list-style-type: none">adjustable within design spacefocus on control strategy and robustnesslifecycle approach to validation, continuous process verification
Process controls	<ul style="list-style-type: none">in-process tests primarily for go/no-go decisionsoff-line analysis	<ul style="list-style-type: none">PAT tools with feed forward and feedback loopsuse of statistical process control methodsprocess 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 processQuality controls shifted upstream; real time release or reduced end-product testing
Product specifications	<ul style="list-style-type: none">Primary means of controlBased on batch data available at time of registration	<ul style="list-style-type: none">Part of the overall quality control strategyBased 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 actionContinual improvement facilitated

adapted from draft Annex to ICH guideline Q8

Figure Legends

Figure 1.

The design space and control space as defined in QbD

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.

Figure 1

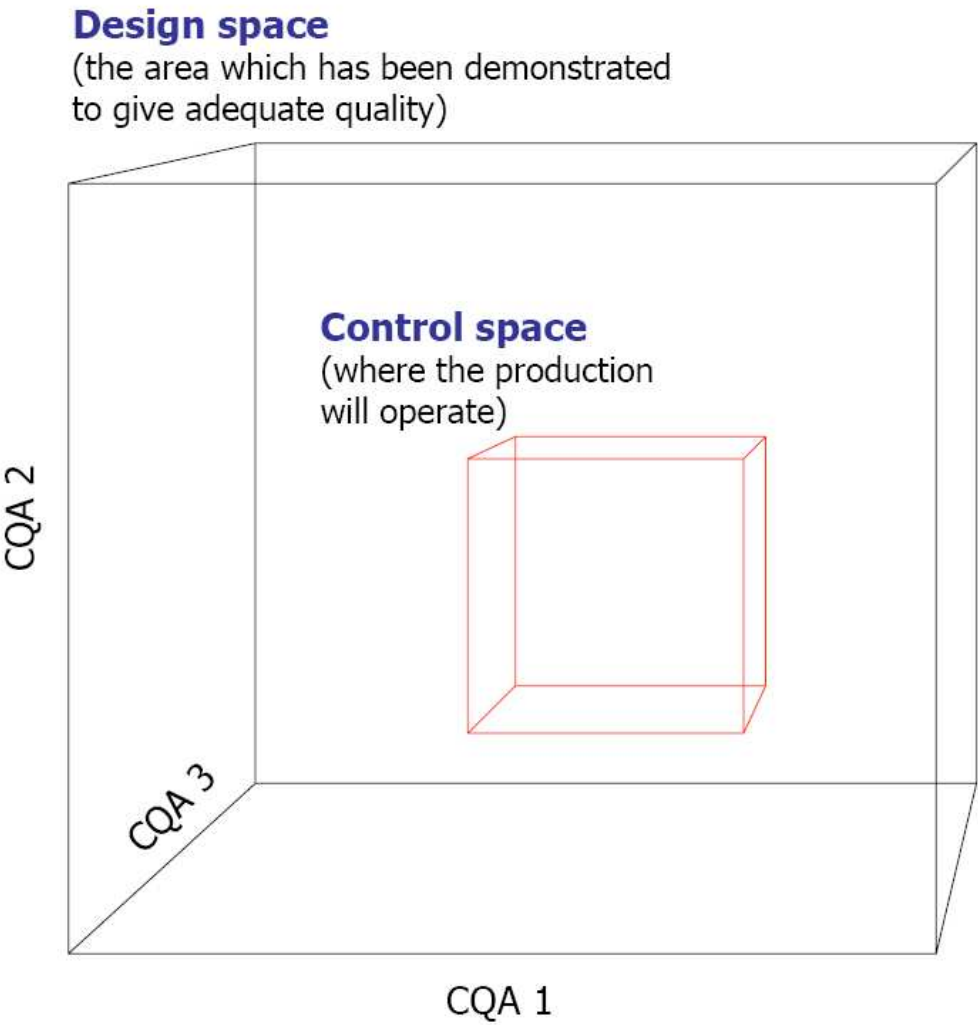


Figure 1. The design space and control space as defined in QbD

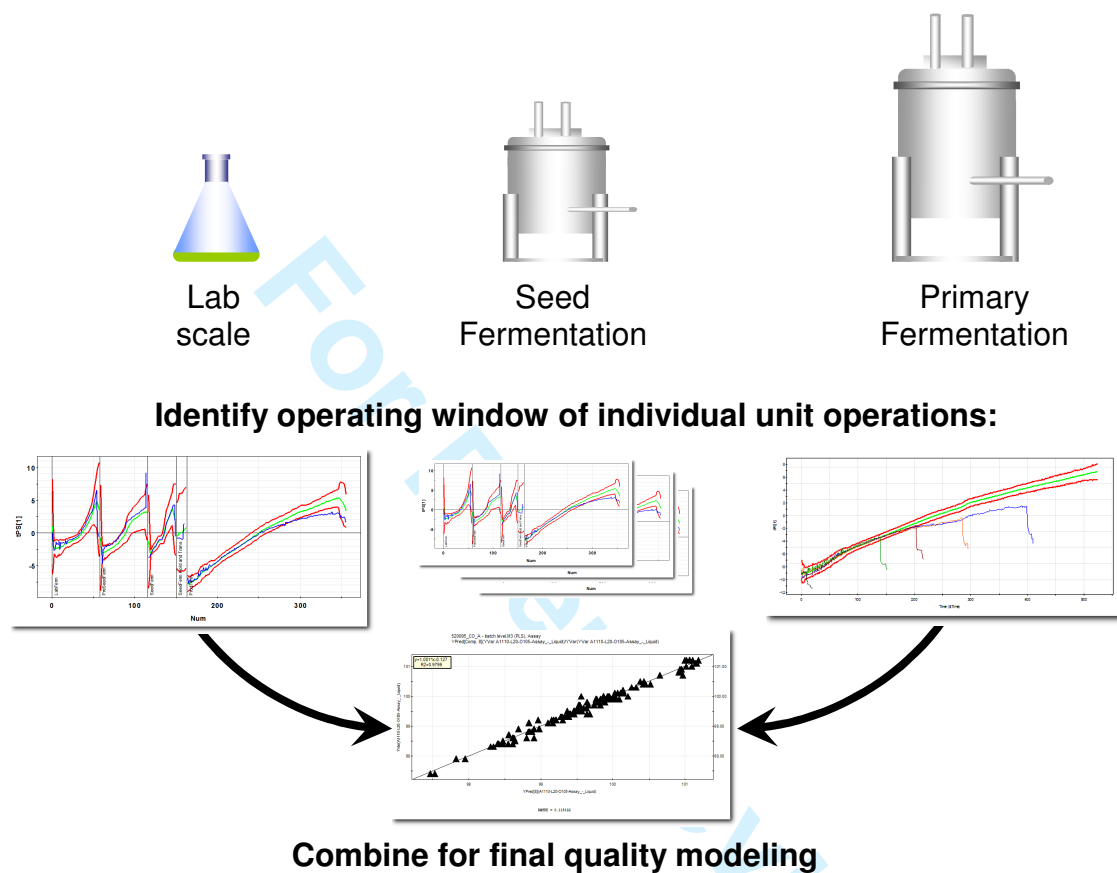
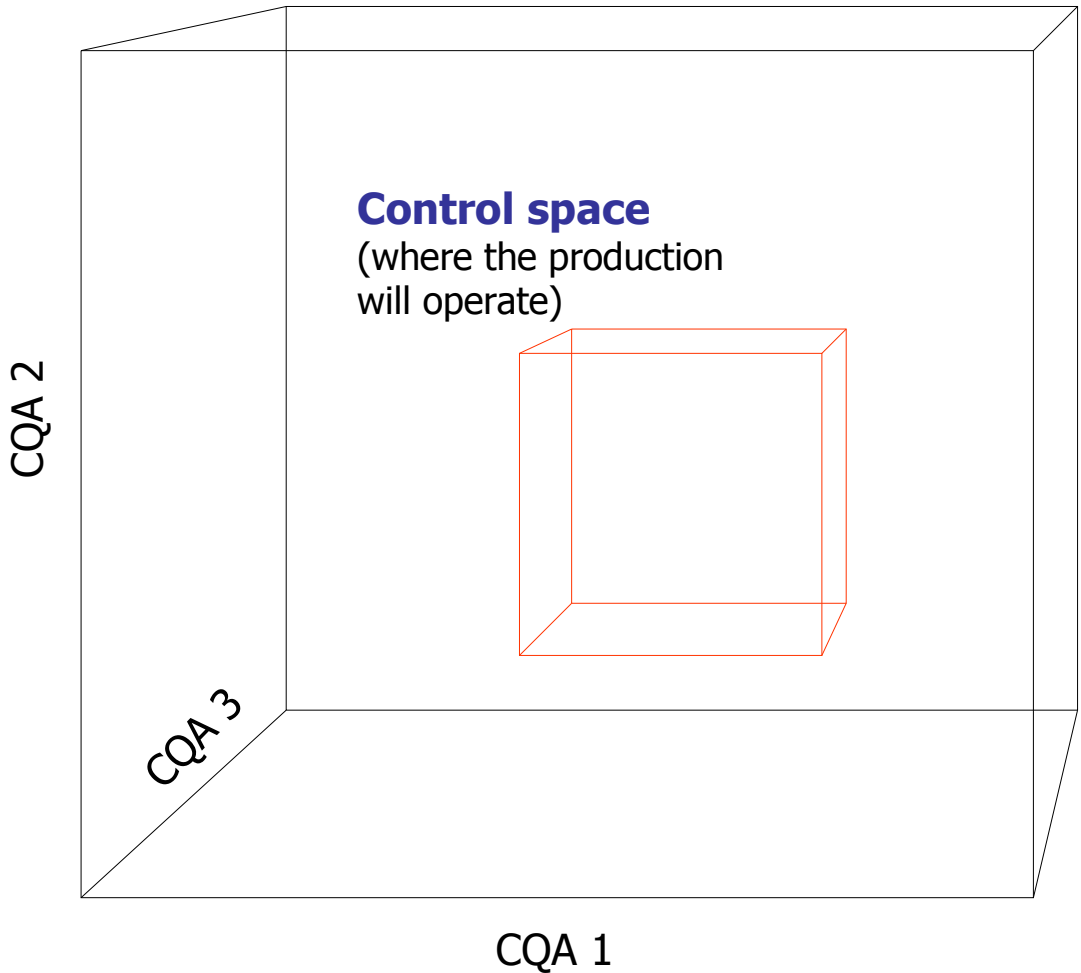
Figure 2

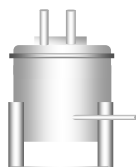
Figure 2. By combining DoE and multivariate data analysis techniques, a multi step process can be summarized in one overview model. This model links the entire history of a lot or batch to its final properties.

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

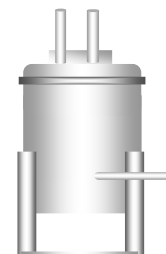




Lab
scale

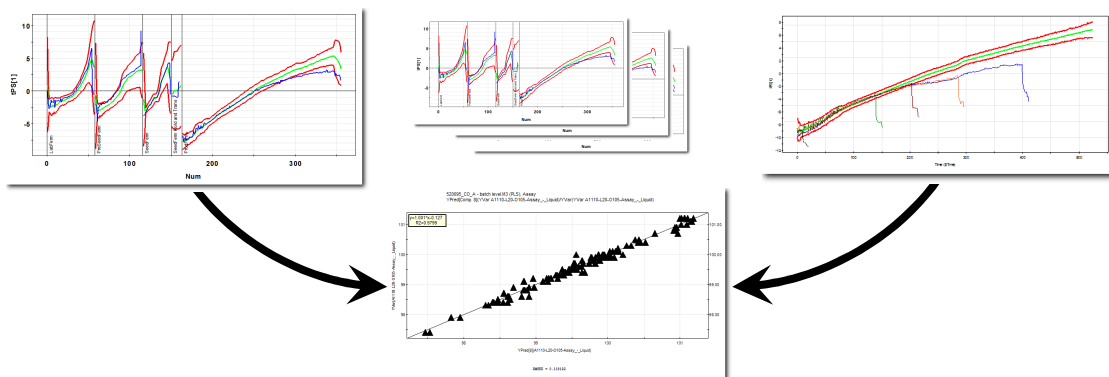


Seed
Fermentation



Primary
Fermentation

Identify operating window of individual unit operations:



Combine for final quality modeling