

# Quality by Design: The Next Phase

## Potential Regulatory Implications and Filing of QbD Data

**Anthony Mire-Sluis, Mark Schenerman, Rohin Mhatre, Siddharth Advant, John Dougherty, Steven Kozlowski, and Wassim Nashabeh, with Lorna D. McLeod**

The first CMC Strategy Forum that focused on quality by design (QbD) was held in July 2007, and it helped establish a general understanding of the various aspects of QbD. Topics discussed included the process for developing a design space for cell culture and purification of a biopharmaceutical product, strategies for filing the design space with regulatory authorities, and potential regulatory hurdles of using QbD data. Continuing with the success of that first QbD forum, the second in July 2008 was designed to provide a venue to discuss progress made by the biopharmaceutical industry in development of QbD concepts and to present updates from regulatory agencies regarding how they propose to review and approve QbD filings.

Case studies were provided by biopharmaceutical companies on the development of design space, PAT applications, comparability protocols, and the proposed use of QbD for routine manufacturing. Regulatory agencies likewise described how they have been approaching QbD filings and potential avenues to regulatory relief for the sponsors. In addition, open forums were held to discuss and obtain consensus on the following issues:

- Based on companies' design space studies, how have validation studies been conducted?

- How have design space data been implemented into process ranges for routine manufacturing?

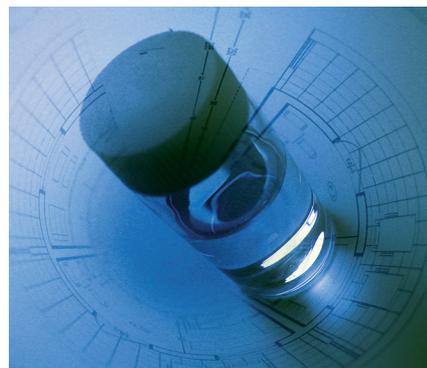
- Do biopharmaceutical companies see a path for regulatory relief based on design space data? Has QbD been a worthwhile effort?

- Have regulatory agencies made further progress in formalizing their review of QbD data?

Those and other relevant questions were discussed at the 2008 interactive forum, 16–17 July 2008 in Bethesda, MD. This forum was divided into four workshop sessions, each involving two to four presentations followed by an interactive discussion with a panel and moderator as well as questions and comments from the audience.

### SESSION ONE: DEVELOPMENT OF CRITICAL QUALITY ATTRIBUTES

On the morning of the first day, Milton Axley from MedImmune discussed strategies for evaluating critical quality attributes (CQAs), describing the risk-assessment strategy his company has developed for determining them. Ron Taticek spoke about Genentech's QbD initiative, including its risk-assessment strategies. Andrew Weiskopf outlined Biogen Idec's work in identifying CQAs and developing a design space for a monoclonal antibody. These three presenters were joined on a discussion panel by Barbara Rellahan from the FDA's Center for Drug Evaluation



**Design space is key to QbD.**

ILLUSTRATION BY CHERYL SCOTT USING  
PHOTOS FROM ANDRZEJ PIKON AND ANDREA GINGERICH  
(WWW.ISTOCKPHOTO.COM)

and Research (CDER). Rohin Mhatre of Biogen Idec moderated.

Much of the 2007 discussion had been devoted to an attempt to define CQAs. Although some variation remains about details, a general working definition has come out of the two forums. CQAs are defined as those attributes that could affect patient safety and product efficacy, regardless of whether we know we can control them. They are generally identified within four main groups: product-related variants, process-related impurities, product composition–strength, and adventitious agents. Most work presented this year involved identifying CQAs within product-related variants and process-related impurities, largely because composition–strength and adventitious agents are generally considered to be CQAs.

## What are the criteria and best practices for developing CQAs and non-CQAs?

In all case studies presented, risk assessments were an integral part of the process of establishing CQAs. Risk assessments are carried out on each identified variant or impurity and used to justify the identification of an attribute as critical or noncritical. When risk assessment did not clearly define criticality of an attribute, directed studies were performed.

Although it is likely that some product-related CQAs may be modality specific (e.g., for monoclonal antibodies) and thus lend themselves to platform understanding, it is important for determining CQAs to understand specific product variants, mechanism of action (MoA), patient population, dosing regimen, and other factors. Each manufacturer must demonstrate what is critical or not for its product and process specifically, thus defining a process- and product-specific control strategy. Therefore, perhaps the concept of “potential” critical quality attributes is useful at the initial development stage. Development work would then focus on providing data to clarify what attributes are or are not critical.

Some attributes, it was agreed, are likely to always be critical, regardless how well we can control them, because of their potential effects on patient safety and product efficacy. These would probably include host-cell proteins (HCPs), DNA, viruses, endotoxin, bioburden, sterility, high-molecular-weight (HMW) species such as aggregates, and content/protein concentration. A wide range of studies were used or suggested as useful to understanding the criticality of product attributes. They included literature; previous platform manufacturing experience; potency assays (cell based, binding, and in vivo efficacy models); pharmacokinetics studies (preclinical and clinical) focused on extracting product from serum and measuring clearance over time; biodistribution; in vitro clearance receptor binding (e.g., FcRN and mannose receptor binding as in vitro surrogates of antibody clearance); complement-dependent

## PROCEEDINGS OF THE WCBP CMC STRATEGY FORUM, 16–17 JULY 2008

The Well-Characterized Biotechnology Products (WCBP) Chemistry, Manufacturing, and Controls (CMC) Strategy Forum was held on 16 and 17 July 2008 at the National Institutes of Health’s Lister Hill Auditorium in Bethesda, MD. Its purpose was discussion of issues related to the concept of quality by design (QbD). As with previous CMC Strategy Forums, the California Separation Sciences Society (CASSS; [www.casss.org](http://www.casss.org)) sponsored this event. More than 150 attendees represented about 30 large and small biotech companies and consulting firms as well as government agencies and academic organizations in seven countries.

Articles based on previous CMC Strategy Forums can be found in the archives at [www.bioprocessintl.com](http://www.bioprocessintl.com). They will be collected in the BPI Extra section to make them easier for readers to find: [www.bioprocessintl.com/bpiextra](http://www.bioprocessintl.com/bpiextra).

cytotoxicity (CDC) and antibody-dependent cell cytotoxicity (ADCC) assays for MAbs; accelerated and/or stress stability studies; and in silico immunogenicity screening. When using literature and previous experience as a basis for evaluating criticality of a product attribute, further discussion and some supporting data may be necessary to provide assurance to regulatory agencies.

**How has the understanding of CQAs and non-CQAs been implemented into development of a design space?** CQAs provide a target on which to focus process characterization, and they indicate where and how to assess whether a process affects a product. CQAs enable selection of operational parameter DoEs for unit operations, which will indicate appropriate process parameters that define the design space. In a risk-based approach, noncritical attributes would draw the least focus during process characterization. However, for process consistency, some level of control of non-CQAs is necessary because a drift in the range of a non-CQA due to process variability could potentially affect the acceptance range of a CQA.

**What is the approach to control noncritical quality attributes?** Even if an attribute is not critical, it would be essential to target a certain range for manufacturing consistency. Although the acceptable range for a non-CQA could be wider than that for a CQA, it is essential to understand how process changes can affect a non-CQA. Variability in multiple non-CQAs, taken together, may affect CQAs.

**How do CQAs evolve during the lifecycle of a product?** Early data from

## PERMANENT ADVISORY COMMITTEE FOR THESE FORUMS

Siddharth Advant (Tunnell Consulting)  
John Dougherty (Eli Lilly and Company)  
Christopher Joneckis (CBER, FDA)  
Rohin Mhatre (Biogen Idec Inc.)  
Anthony Mire-Sluis (Amgen, Inc.)  
Wassim Nashabeh (Genentech, Inc.)  
Nadine Ritter, chair (Biologics Consulting Group, Inc.)  
Mark Schenerman (MedImmune)  
Keith Webber (CDER, FDA)

research can provide “presumptive” CQAs at the investigational new drug (IND) phase with risk assessment in absence of extensive data. How much can be defined at early stages depends on the maturity of QbD efforts during research. A thorough understanding of the mechanism of action, an appropriate level of analytical characterization, and an understanding of other relevant quality attributes will lead to a clearer picture at the IND stage.

Nevertheless, early in development it is difficult to determine with certainty which attributes are critical, particularly among product-related variants. There was no clear consensus on whether a term other than *critical* should be applied to those attributes in early phases (such as *presumptive* or *potential*) or whether they should all be treated as critical until a development process proves them to be noncritical. There was consensus, though, that beginning with the end in mind is valuable.

During development, quality attributes will gain more accurate definition as actual data accrue and a

company learns more about its product's mechanism of action or obtains preclinical and clinical data. In a marketing application, CQAs identified during risk assessments are included in defining and justifying product specifications. After licensure, CQAs may be refined as more data become available.

**How could the understanding of CQAs affect the development of product specifications?** A CQA is probably more likely than a non-CQA to require a specification. However, even a CQA may not require a product-release specification if it is well controlled or cleared within the process based on process validation studies. Examples would include residual DNA, protein A, or HCPs. Conversely, a non-CQA may require a specification if it is used to measure process consistency; if it is a compendial, regulatory, or "standard" quality assurance requirement (such as 10 ng/dose DNA); or if its risk/benefit ratio to patients must be monitored.

## **SESSION TWO: DEVELOPMENT OF DESIGN SPACE**

Thursday afternoon's presentations and subsequent panel discussion focused on development of design space. Siddharth Advant of Tunnell Consulting moderated, and presentations were given by Steven Kozlowski of CDER, Helena Makagiansar of Biogen Idec, Greg Blank of Genentech, and Adeola Grillo of Human Genome Sciences. Susan Kirshner of CDER joined the presenters on the discussion panel.

**Are companies using a consistent approach for developing design space?** Early in a development process, companies are aiming to define a target product profile (TPP), which will encompass both product- and process-related substances and impurities. Understanding that the process will be iterative, you define your profile as well as you can and adjust it as you gain knowledge by working through the unit operations.

A design space is developed at small scale using design of experiments (DoEs). Data derived from large-scale manufacturing are then used to assess

## **2008 FORUM PRESENTATIONS**

"Strategies for Evaluation of Quality Attributes," by Milton Axley of MedImmune (Gaithersburg, MD)

"Critical Quality Attributes: Defining and Applying Them in the Product Lifecycle" by Ron Taticek of Genentech, Inc. (South San Francisco, CA)

"Identifying Critical Quality Attributes for Development of Design Space for a Monoclonal Antibody Therapeutic" by Andrew Weiskopf of Biogen Idec Inc. (Cambridge, MA)

"Approaches to QbD Design Space for Biotechnology Products" by Steven Kozlowski of CDER at FDA (Bethesda, MD)

"Design Space for a Late Stage Antibody Production" by Helena Makagiansar of Biogen Idec Inc. (Cambridge, MA)

"Design Space for Purification Processes: Challenges, Opportunities and Strategies" by Greg Blank of Genentech, Inc. (South San Francisco, CA)

"Evaluation of the Formulation Design Space Using DOE" by Adeola Grillo of Human Genome Sciences, Inc. (Rockville, MD)

"Regulatory Considerations for Quality-by-Design Submissions" by Barry Cherney of CDER at FDA (Bethesda, MD)

"Application of QbD Principles to a Major Process Improvement for the Manufacture of a Recombinant Therapeutic Protein" by Enda Moran of Wyeth Biotech (Grange Castle, Ireland)

"Leveraging QbD for Regulatory Relief" by Suzanne Stella of Biogen Idec Inc. (Research Triangle Park, NC)

"ISPE PQL: Applicability to Biotech" by Ron Branning of Gilead Sciences Inc. (Foster City, CA)

"The EFPIA 'Mock S2 for Biotechnology Drug Substances' Project" by Brendan Hughes of Wyeth BioPharma (Grange Castle, Ireland)

the validity of the small-scale models. However, you must consider whether all factors and variables have been identified, let alone explored, during DoEs. The most relevant DoE studies using small-scale models appear to be those that include multivariate interactions. It is unlikely that all possible interactions that could occur during routine manufacturing at scale can be explored. The variability of multivariate parameters at scale can be

analyzed over time to "validate" a small-scale model. Some companies have enough experience to develop "platform small-scale models" in which data from other molecules can be applied if doing so is appropriately justified.

**What risk assessment tools are being used?** The risk-assessment tools most commonly used are prospective and semiquantitative with predefined ranking or scoring. Such tools require a multidisciplinary team of experts. The areas of expertise involved depend on the proposed use of a risk assessment — for example, evaluating a single unit operation or defining critical performance parameters (CPPs) and CQAs. Working with a trained facilitator who is expert at using risk-assessment tools is recommended.

Methods used include risk ranking; hazard analysis and critical control point (HACCP) analysis, hazard operability (HAZOP) analysis, failure modes and effects analysis (FMEA), preliminary hazards analysis (PHA), and others. Most of these tools use effects or consequences and probability as the main considerations for criticality scoring.

A company may use one risk assessment to select which parameters to investigate as definitive parameters for DoE and another, based on DoE data, to understand criticality. It is important to understand what you are using risk assessment for and its objectives. Each assessment tool offers advantages and disadvantages and should be properly selected.

Identifying quality attributes first is vital to successful risk assessment. Therefore, a company's analytical understanding of its product should be reasonably mature before a design space is developed.

**How has data generated during design space development been implemented into process ranges for routine manufacturing?** Through QbD and your design space, you should be able to move from a control paradigm with large numbers of control points and tight limits to one with controls that are individually and collectively more meaningful for obtaining desired product quality. The objective of design space development

is not necessarily to define wider process operating ranges, but to justify adjusting those ranges defined in a batch record based on further understanding of the process and resulting in a better yield, changes in critical raw materials, or introduction of new equipment. In either case, all changes to the process ranges will have to be made within the established design space. Furthermore, confirmation of a desired product attribute should also be considered for process changes within the design space at a manufacturing scale.

**How are validation studies being conducted based on knowledge gained from a design space?** Using the concept of the TPP, you can develop a product design space leading to the rational design of a protein product that has few or no heterogeneity or stability issues (e.g., design out oxidation or deamidation sites, improve tertiary structure, reduce potential for aggregation). Reduction of product variants lowers both the number of CQAs and the possible impact of a process on CQAs, thus reducing the number of possible critical process parameters as well as the number of controls that need to be validated. Development of a design space allows for an understanding of critical and noncritical performance parameters, thus allowing for the focus of validation studies on parameters that are important for product quality.

Development of a design space also allows for wider validation acceptance criteria because the range of control within which product and process are unaffected is better understood (and presumably wider) than a range set empirically on manufacturing experience alone. However, “classical” process validation using conformance runs involves a manufacturer running its process at central set points, so design space really has no effect on “validation acceptance criteria” because we never actually “validate” any ranges during conformance runs. You could use a quality system to control movement within a design space in a protocol-type validation program. But this may be impractical because there are too many parameters to evaluate,

and no company will take the risk of running different ranges at large scale.

### **SESSION THREE: QbD REGULATORY SUBMISSION STRATEGIES**

On Friday morning, 17 July 2008, John Dougherty of Eli Lilly moderated the third workshop. Barry Cherney of CDER, Enda Moran of Wyeth, and Suzanne Stella of Biogen Idec made presentations. Sally Anliker from Eli Lilly, Joseph Kutza of MedImmune, Jennifer Mercer of Amgen, and Patrick Swann of CDER joined the presenters on the panel for a discussion of regulatory issues surrounding QbD.

The Office of New Drug Quality Assessment (ONDQA) pilot submissions have focused mainly on drug product, particularly individual unit operations. So it would be essential to include submissions for drug substance and formulation design space in the planned Office of Biotechnology Products (OBP) pilot. ONDQA submissions identified critical quality attributes and linked them with process parameters and incoming material attributes. However, submissions exhibited a gap in successfully summarizing prior knowledge. Risk assessments were a central theme but were too limited in scope, and their outcomes — risk mitigation — were not well addressed. Some submissions used DoE to define a design space, but the design space was not applied to potential scale-ups and site or equipment changes.

**What experiences and learnings from the ONDQA pilot (2005) can apply to the OBP QbD pilot from both industry and FDA perspectives?** PAT concepts were included in a few ONDQA submissions but were not built into manufacturing processes or lot release. Companies used data concerning CQAs, design space, and risk assessments to establish sound control strategies that ensure consistent product quality and process performance. However, there was a lack of substantive information used to develop specifications, including the rationale for test selection and sampling plans. Basic QbD concepts were not fully accepted by regulators (e.g., use of

clinical data and CQA understanding to set specifications). The “comprehensive” quality overall summary (QOS) did not appear as useful as expected and was not applicable as a primary review document.

The submission of expanded change protocols (ECPs) will be valuable, including those that cover changes to a process across unit operations, scale, equipment, and facilities. For scale changes, you need to ensure that design space defined by small-scale models will be scalable to large-scale manufacturing. Movement within a design space is usually shown not to affect product at small scales. Questions remain regarding how to ensure that scaled-up processes respond similarly.

Forum participants expressed interest in how an OBP application will result in regulatory relief or agreements, which remains an open question. One participant commented that the increased interactions of cross-functional internal company organizations (e.g., research, development, clinical, quality, and regulatory groups) were extremely valuable in one company’s ONDQA (mock submission) experience. Understanding product and process on the level required of and resulting from a QbD filing creates a need for greater interaction and cooperation among company organizations than most companies are accustomed to having.

It was generally agreed that full agency engagement during review is necessary for pilot success, particularly considering the review timelines. In real-time, opportunities for presubmission discussions with the agency will arise, and experience has shown this to be very valuable.

**How should the pilot program address regulatory review of QbD submissions that ultimately involve close cross-functional collaboration between divisions, including the Therapeutics Facilities Review Branch (TFRB) of the Division of Manufacturing Product Quality (DMPQ)?** The pilot program and

QbD concepts need to be integrated across the FDA including its Office of Biotechnology Products (OBP), Office of New Drugs (OND), Office of Compliance, and Office of Regulatory Affairs (ORA). For the pilot, the Office of Compliance will be part of review communication, so there is a need to transfer information among OBP, OC, and the field. Ideally, product reviewers should be present at initial QbD-type inspections. The Office of Compliance will play a key role in understanding the role of quality systems in QbD filings and their control strategies.

For an original application or supplement, it is believed that an ECP can be used for describing a process design space, control strategy, and risk-management plan with a link to CTD sections containing supporting information. **Does this forum believe that will facilitate submission and review?** An ECP will present a valuable opportunity to expand beyond the traditional comparability protocol approach of a single change with well-defined acceptance criteria. However, it is unclear what the design space inclusion in such a filing and its role in an approval “contract” should look like. Is it a list of CPP ranges? If the design space does not include data relevant to equipment changes, scale changes, or facility changes, then should they be reported? No clear consensus was reached for the long term, but for early QbD submissions the answer is most likely “yes.”

**Other ICH regions do not allow for the use of protocols, so how can we use this approach to develop core dossiers for global implementation?** Participants discussed attempting to develop a “global QbD submission” by including QbD data in the CTD format, with minimal changes for those agencies not generally following QbD principles. However, the CTD format is not optimal for QbD flow. Preferring the idea of possible changes to the CTD, the forum agreed that it would be hard to achieve. So it was suggested that

perhaps using the electronic format can allow for a QOS to serve as the summary and table of contents that electronically links to module 3. However, there appears to be no general support for a postmarketing plan within EMEA.

QbD data can be included in QbD filings, but it is up to each company to negotiate “acceptability” of any agreement based on such information. There was discussion about what exactly constitutes the “contract” between a company and a regulatory agency, which remains unclear at this point.

**What does the industry see as the difference between an “Expanded Change Protocol” and a “Comparability Protocol” to facilitate the submission of QbD information?** ICH Q5E should apply to both protocols, but traditional comparability protocols focus on whether a product is “comparable after a process change,” with product testing as the central theme. An ECP is a more holistic document that assures not only product comparability, but also that the control strategy of a changed manufacturing process remains in place and applicable.

Development of a change control plan filed in the regional information section targets the more “GMP” aspects of how an expanded protocol will be used — including the concept of a “change space” (defining to what the protocol will apply). Unlike traditional comparability protocols, how a change will be evaluated on a more expanded basis must be assessed, including the application of understanding CQAs, CPPs, and CMAs for raw materials. Risk assessments are not always included in justification of traditional comparability protocols, but they would be necessary for an ECP. It can also include what actions would be taken if acceptance criteria are not met.

Participants agreed that it will be important to clarify the role of a quality system in assuring that changes are managed appropriately, particularly for those that do not

require a regulatory inspection under a QbD system.

**From an industry and FDA perspective, how are risk assessments incorporated into QbD submissions?**

Risk assessments are being used at a minimum for understanding the criticality of quality attributes, for selection of process inputs used in DoE studies for design space, for developing CPPs based on process characterization, and for justification of specifications. The level of detail pertaining to prior knowledge, available data, the basis for criticality scoring, and other factors to be included in a submission based on risk assessment is not clear. There has to be sufficient detail for a reviewer to understand how the high-level conclusions were derived. As stated, however, reviewers were not fully accepting of QbD concepts in the ONDQA mock, so it is likely that more rather than less detail may be required in early QbD filings.

**Does this forum support establishing a task force to develop a guideline for sponsors to understand how to use risk assessments, including development of a risk-management plan related to overall control strategy?** Clearly risk assessments are becoming a central and expected part of product development. Guidance on which risk analysis tools to apply in particular situations would be extremely valuable. Companies also need to understand how best to include risk assessments in developing their overall control strategy for a product and what to include in associated regulatory filings (CQAs, CPPs, specifications, in-process controls, or IPCs) linking multiple assessments. So a task force to define how to present a risk assessment would be welcomed.

Considerable FDA and industry effort has been put forth to develop a common understanding of QbD concepts and the complexities involved in obtaining regulatory relief. **After several collaborative interactions and meetings, does this forum believe that the progression**

**to date will ultimately arrive at that common goal?** It appears that regulatory relief in the form of decreased filing requirements before making changes is in sight provided that the OBP pilot is successful. However, companies will benefit from QbD whether or not it provides regulatory relief because it will lead to better process understanding, reduced risk for process changes, and more robust manufacturing processes.

The extent to which manufacturing flexibility using design space will be implemented depends on how design space will be defined in filings and how agencies “approve” it. The role of inspections following QbD filings or changes is unclear at present. Debate is ongoing about how a filing becomes a “contract” that defines what is reportable as a change and what is not.

#### **SESSION FOUR: MOCK CASE STUDIES**

On Friday afternoon, Steven Kozlowski of CDER moderated and spoke briefly about the CMC Biotech Working Group led by Conformia Software Inc. ([www.conformia.com](http://www.conformia.com)), which is working to create a mock submission exemplifying QbD. Presenters were Ron Branning of Gilead Sciences and Brendan Hughes of Wyeth. They were joined on the panel by Roman Drews of FDA’s Center for Biologics Evaluation and Research (CBER), Chana Fuchs of CDER, and Joseph Phillips of Amgen, to discuss past, ongoing, and upcoming mock QbD submissions.

**What areas would be important to cover in a biotech QbD mock case study, and what is a reasonable level of detail?** Mock submissions should provide the information required to understand both a product and its process. These submissions should be transparent about the logic and rationale used by a sponsor during development and present data to illustrate robustness and relevance. The ideal mock case study would include a rational strategy for

building and mining process knowledge, defining what is critical, and capturing potentially relevant information. It would exemplify scale-down models and multifactorial experiments and illustrate control strategy. Its design would include patient and business considerations as well as manufacturing. And defining postapproval changes may be advisable within a mock case study.

Such “mocks” are urgently needed to provide examples and guidance to both sponsors and regulators. A successful mock case study would serve as a guidance for industry in operating within boundaries and a template for discussion with authorities. Once these mocks have been done and their results discussed widely, they could lead to a faster path for review and approval and greater regulatory flexibility.

Obviously, different sponsors may take different approaches. Ideally, there should be a number of different mock case studies covering a range of different products and manufacturing scenarios. As the mocks are designed and carried out, it is important to keep in mind that design space is a living document and should be periodically reviewed within a quality system. CQAs may evolve over time as greater process and product knowledge is gained, and mock case studies may illustrate that evolution. Additionally, the mocks will undoubtedly stimulate further discussion about the level of detail needed in QbD submissions.

The document produced by a mock filing would not constitute endorsement by the FDA, nor is it intended as a gold standard. The agency would like to see documents with depth rather than miniature case studies. Articles published on various QbD topics for small molecules may provide some basis for biotech publications when the time comes.

**Current Progress:** ISPE’s ongoing Product Quality Lifecycle Implementation (PQLI) mock is attempting to bring industry and regulatory groups together to define

issues on implementation of ICH Q8–10 on pharmaceutical development, quality risk management, and pharmaceutical quality systems ([www.ispe.org](http://www.ispe.org), [www.ich.org](http://www.ich.org)). The European Federation of Pharmaceutical Industries and Associations (EfPIA, [www.efpia.org](http://www.efpia.org)) Mock S2 was shared in Europe in early 2008; it remains a work in progress. Teams were formed in 2007 for a biotech mock case study. Mock QbD inspections held in Ireland were very useful in building understanding between industry and regulators and may help in better defining ICH Q11 on development and manufacture of drug substances (both chemical entities and biotechnological/biological entities).

Conformia has just begun working toward generating a mock biotech submission. One premeeting was held as part of an FDA cooperative research and development agreement (CRADA). Conformia intends to draft a MAb mock case study in 2008 and a vaccine mock case study in 2009. A mock case study for therapeutic proteins has yet to be defined.

**What areas would be important to cover in a biotech QbD mock case study? What should be the type of content?** The broad goals listed above for an “ideal mock” would necessarily encompass an equally broad range of content. The mock case study should define terms clearly, examine life-cycle management and regulatory impact, and result in a better understanding of the science behind a product and its process. Specific details will depend on the types of manufacturing steps being used. Detail should match the complexity of the process. Several different types of approaches could be included in the same mock case study to answer a range of questions. Clearly, the most important consideration is to include enough detail for both regulators and industry to understand the approach (or approaches) thoroughly. To ensure that, it will be valuable to

keep in mind from the beginning the typical questions heard from regulators during previous mocks.

Some underlying assumptions will have to be made to keep such a filing manageable. They have to be justifiable to regulators and thus be stated and justified early in the process. Some specific content participants mentioned for inclusion was a TPP, CQAs, critical performance parameters, process design, design space, control strategy, risk assessments (along with their justifications and results), prior knowledge, QbD across product classes, quality system monitoring, linkages to raw materials, expanded descriptions of individual unit operations, and a description of the modular approach to viral validation (if applicable). The level of detail should be defined through a mock submission discussion with the FDA during preparation.

**Should a mock case study focus on QbD for unit operations or an entire manufacturing process?** Considering the complexity of an entire manufacturing process, early mocks should focus on one unit operation. Each unit operation mock could focus on risks associated with a particular operation as well as accumulated risks created through its interaction with the rest of the process. Keep in mind that such accumulated risk may come from interactions with other operations throughout the process, not just those immediately adjacent to one another. Ultimately, however, a manufacturer must assess its whole process for the overall control strategy to be meaningful.

**What approaches would get the most benefit from mock QbD biotech submissions?** The forum agreed that industry consortiums are the best approach for maximizing the benefits of mock QbD submissions. Drafts of the resulting mock case studies should be circulated broadly for the greatest amount of input. Such drafts could be reviewed at global conferences and posted on the Worldwide Web. It would be useful to create a forum for discussing

progress on all the mocks.

## RELIEF IS POSSIBLE

Although questions remain (e.g., exactly how the FDA will approve a design space, the level of detail necessary in a QbD filing, and others), both industry and regulators seem closer to a workable definition of CQAs than they were a year ago. Mock submissions are being developed that will give the biotechnology industry an opportunity to work through some questions about QbD filings that were not answered in the small-molecule mock case studies. Companies are beginning to integrate QbD concepts into their processes, a move that will provide benefits including better product and process understanding and, ultimately, regulatory relief. 🌐

*Anthony Mire-Sluis is executive director of global product quality at Amgen, Inc.*

*Mark Schenerman is vice president of analytical biochemistry at MedImmune. Corresponding author Rohin Mhatre is senior director of biopharmaceutical development at Biogen Idec Inc., 14 Cambridge Center, Cambridge, MA 02142; 1-617-679-2031; rohin.mhatre@biogenidec.com. Siddharth (Sid) J.*

*Advant is principal at Tunnell Consulting, Inc. John Dougherty is a regulatory advisor in regulatory affairs CM&C at Eli Lilly and Company. Steven Kozlowski, MD, is with FDA's Center for Drug Evaluation and Research. Wassim Nashabeh is director of CMC regulatory affairs at Genentech, Inc. Lorna D. McLeod is a contributing editor for BioProcess International.*

## DISCLAIMER

The content of this manuscript reflects discussions that occurred during the CMC Forum workshop in addition to the personal viewpoints and experiences of the authors. This document does not represent officially sanctioned FDA policy or opinions and should not be used in lieu of published FDA guidance documents, points-to-consider documents, or direct discussions with the agency.