QbD for Biologics

Learning from the Product Development and Realization (A-MAb) Case Study and the FDA OBP Pilot Program

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Cosponsored by CASSS (an international separation society) and the FDA, the 23rd CMC Strategy Forum was held in Bethesda, MD, on 19–20 July 2010. For the third time, this forum explored the topic of quality by design (QbD) for biologics. The first such forum was held in July 2007 and focused on establishing a general understanding of QbD terminology and concepts. In July 2008, the second discussed approaches for submission of QbD data and associated regulatory implications. Building on those previous QbD forums, this third forum extended the discussion from "what" to "how." The program committee intended to cover detailed implementation strategies and practical key QbD elements that are readily achievable in the short term.

In addition, this forum would combine key learning from two important QbD industry–FDA collaborations: the A-MAb Case Study and the FDA OBP Pilot Program. The pilot program is still in its early stages but nonetheless provides concrete examples of the types of exchange of ideas between sponsors and regulators. The case study on applying QbD principles in development of a monoclonal antibody represents the culmination of a two-year effort by a consortium of biotechnology companies collectively known as the CMC-Biotech Working

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Group. The companies involved were Abbott Laboratories, Amgen, Genentech, GlaxoSmithKline, Eli Lilly and Company, MedImmune, and Pfizer. To ensure free public access and further promote the industry-wide discussions that led to its creation, they provided its case study to CASSS and ISPE. Find it online at www.casss.org/associations/9165/files/Case_Study_Press_Release.pdf.

This forum was set up as three workshops covering quality attributes, design space (DS), and control strategies. Authors of the A-MAb case study and sponsors participating in the FDA Pilot Program provided detailed QbD examples to form the basis for workshop discussions. A number of questions were presented as a basis for discussion, and they appear in bold throughout this text.

Critical Quality Attributes (CQAs)

In assessing attribute criticality, to what extent is it appropriate to apply prior knowledge from similar-class molecules to a new product? When is it appropriate to leverage company-specific and literature information?

Leveraging prior knowledge is particularly valuable at the earliest stages of development before you've had a chance to gain molecule-specific data in early development. Prior knowledge of molecular structure at early stages is useful for highlighting specific product variants you need to look for and targeting the types of analytical methodology required to assess them. As long as its strengths and weaknesses are understood, information is valuable wherever it comes from.

Keep in mind that, although general assumptions can be made about class-specific attributes (e.g., MAb terminal heterogeneity), inevitably some molecules will not follow the rules. The value of general assumptions depends on the depth that knowledge can reach — how

specific it is to your particular molecular structure/function. For example, what about its glycoform structure does or does not affect Fc receptor binding?

Is the biotech industry still excited about QbD, or are anxiety and frustration replacing excitement? Instead of managing risk, are we becoming more risk-averse? Some consensus was reached that QbD is a good idea in theory, but there is still work to be done in clarifying what it is and how it is best used. Although the idea is to have a DS within which changes can be made without formally reporting them to regulators, it appears at present that more documentation (rather than less) is probably needed. As one regulator pointed out, "If we had total trust in a DS, we wouldn't need regulatory agencies."

It was generally agreed that we need an adaptable way of assessing reportability criteria with a common understanding of what needs to be provided, both in a filing and in terms of changes. How much can be handled by a company's quality management system (QMS), or pharmaceutical quality system (PQS) according to ICH Q10? How much documentation will ensure regulators' comfort level?

As far as enthusiasm goes, it was noted that QbD needs to have inherent value to a company to make it worthwhile. It is a good, progressive idea, but companies need to understand its value to them and see it making sense from both science and business perspectives to maintain their enthusiasm. Regulatory relief (one of QbD's original drivers) is still a future prospect.

How much additional molecule-specific information would be required to support an assessment based on prior knowledge? It is unlikely that the criticality of quality attributes for a given molecule will be identical to that of another molecule. So it is worthwhile in investigating the unique aspects of a molecule to confirm assumptions about "class-specific" knowledge. Whether to check all relevant attributes while looking at their effects on pharmacokinetics (PK) or pharmacodynamics (PD) often depends on a number of factors: e.g., the scope and significance of class-specific knowledge and the availability of meaningful models. Other factors to consider are different dosing regimens (e.g., intravenous or subcutaneous), chronic or single dosing, patients' disease state including whether patients are immunosuppressed, and so forth. When changing a molecule's indication, you must revisit your CQA risk assessment.

This question remains: **At what point can we accept an attribute as noncritical for all class-specific molecules?** Regulators are at present reluctant to allow such an assumption across the board, so justification is required case by case. One participant put it very succinctly: "Literature and knowledge can be a wealth of data if the data are relevant to your molecule." Proving that literature is relevant is important for the comfort of regulators and for ensuring that your product is truly safe and efficacious.

There was also discussion about which parts of a QbD submission constitute regulatory commitments and what can be handled through a company's pharmaceutical quality system (PQS). There is no definitive answer. Early and frequent consultations with regulators are recommended, and "negotiations" with the agency are to be expected.

In setting and justifying acceptable ranges for CQAs, what information is required? When are preclinical data sufficient, and when are clinical data required? The value of preclinical data depends on the animal model used. Questions that need to be asked regard its relevance to humans, whether the ligand/target has the same properties as in humans (including PK and PD effects). How does the disease state in humans affect how you interpret and use the data? Do immunogenic responses in animals affect your evaluation? Although an advantage of preclinical testing is in exposing animals to purified variants, clinical data are still the gold standard as long as patient variability considered. Extracting product from serum samples is very valuable and informative for PK.

However, the utility of clinical data for PD depends on available markers (e.g., increasing blood-cell levels are easier to measure than tumor size/s or overall survival). Again, although general assumptions can be made (e.g., MAb terminal heterogeneity), inevitably a case will arise with molecule-specific differences, and ranges for those will need to be justified. CQA ranges depend on manufacturing process capabilities, patient populations, dose strategies, and so on. It seems difficult to justify a single range for a particular CQA across a whole class of molecules; only DNA and endotoxins seem to have achieved that from a safety perspective. However, it appears that the CQA risk-assessment tool now used across the industry is seen as an effective mechanism for incorporating prior knowledge. But "noncritical" or "less critical" QAs must still be considered in relation to CPPs and their related control strategy with

The CMC Strategy Forum Series

The CMC Strategy Forum series provides a venue for biotechnology and biological product discussion. These meetings focus on relevant chemistry, manufacturing, and controls (CMC) issues throughout the lifecycle of such products and thereby foster collaborative technical and regulatory interaction. The forum committee strives to share information with regulatory agencies to assist them in merging good scientific and regulatory practices. Outcomes of the forum meetings are published in this peer-reviewed journal with the hope that they will help assure that biopharmaceutical products manufactured in a regulated environment will continue to be safe and efficacious. The CMC Strategy Forum is organized by CASSS, an International Separation Science Society (formerly the California Separation Science Society), and is cosponsored by the US Food and Drug Administration (FDA).

justification as to how they were considered (not forgotten).

Kowid Ho discussed how the European Union (EU) PAT team is and is not implementing QbD concepts. One complication in Europe is the existence of two entities — the Council of Europe and the European Union — which include different countries and do not always agree about issues related to drug applications. The European Medicines Agency (EMA) represents the EU's 27 member nations and has taken on the task of regulating how drugs can move across national borders. So the answer to "what is required" can vary depending on which agency is involved.

In setting and justifying acceptable CQA ranges, what information is required? How does stability fit in? Stability must be considered for comparing levels of attributes present at time zero with those that may change over time until expiry. Thus patient exposure to end of expiry material must be considered when establishing ranges (especially if used in clinical studies). You also must account for the appearance of new attributes as a product degrades over time, which could necessitate adding quality attributes (and setting an appropriate ranges) to your preliminary quantitative risk assessment (PQRA) that are not present at time zero.

In setting and justifying acceptable CQA ranges, what information is required? How do we reconcile the value of establishing broader clinical exposure to product variants with the goals of product development, which continually drives toward comparability, consistency, and higher purity? Producing "more variable" product lots early in development can provide patient exposure information and help you understand the impact of different levels of attributes on PK/PD (and maybe safety). But such variability may not reflect commercial process capability, especially at the time of licensure, although it may be important for future changes and provides for an expanded CQA "DS." There is, of course, an increase in cost and time associated with producing greater numbers of smaller lots early in development. Using lots enriched for a specific variant early in development is another route toward understanding QA criticality. However, keep in mind whether you can justify patient exposure to potentially negative affects resulting from levels of attributes beyond what is normally designed into dose-escalation studies.

How does a company broaden CQA ranges based on safety and efficacy considerations? The assumption is that a "critical quality attribute" will affect safety and efficacy. So you have to understand at what point an effect is relevant to patients (e.g., aggregates). Shed light on this question by leveraging preclinical and clinical serum samples for detecting variant clearance over time and for maximizing assessment of dose-ranging studies. Linking QA levels to immunogenicity, safety, and efficacy is challenging. Most current clinical studies are not designed to link specific levels of attributes to patient outcomes. If possible, strategies for better correlating quality attributes and clinical data would be valuable.

Epitope mapping can be useful if you see an immune response. By introducing increased levels of attributes into an appropriately powered preclinical study, you can discover what levels have an effect. Relevant in vitro studies can show limits that do or do not affect PK/PD (e.g., Fc receptor binding, potency assays, and so on). Data derived from the clinic may lead to attempts to reduce the levels (or strengthen control) of a given attribute if the link of safety/efficacy to a QA can be made after the original risk assessment.

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As in previous QbD forums, there is still a good deal of uncertainty about terminology. ICH Q8R defines QbD as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management." Some commenters consider that definition to be too vague. In addition, there is still a wide range of working definitions of CQAs, particularly at the earliest stages of development. One company calls them "provisional" CQAs; other terms have been discussed at previous forums. It is difficult to work within definitions you aren't clear about.

What aspects should be considered when assessing interactions between quality attributes? Can the interaction of noncritical attributes render them critical? What information would be required to establish an absence of interactions? You could use the DS of fermentation, for example, to get an idea of the true "DS" in relation to relative levels of QAs being produced before needing extensive interaction studies of QAs that are not realistically manufactured at different levels by your process. Some attributes on their own may not appear critical but then interact and become critical, although no specific examples were mentioned. You can use forced degradation to create high levels of a particular QA (e.g., oxidation) and examine its impact on another (e.g., aggregation) to determine whether their interaction is raising the criticality level. It will require creating a range of purified molecules with each QA at specified levels and testing them in animals or in vitro (if feasible) to show a lack of impact on PK/PD (and maybe safety). But that can be extremely costly and time consuming.

Design Space

What types of information/data can be used to define a DS (e.g., manufacturing data, design of experiments, platform/prior knowledge)? Manufacturing data from pilot-scale runs, engineering runs, and full-scale clinical and/or commercial

runs can be used in defining DS. Design of experiments (DoE) and process characterization are also useful, as is platform or prior knowledge including both internal and published (external) data. Formulation development will yield useful data, as will stability and comparability studies. All those product-related data should be included in assigning criticality to quality attributes.

Literature should be used carefully. In-house data are more valuable than peer-reviewed published literature because they can be backed up and their history verified. The quality of data in published papers varies significantly. Conclusions based on literature, in-house or otherwise, should be confirmed for a new molecule. Some assumptions can be made safely, particularly for a platform product. But anything unexpected must be investigated.

Should a DS consist of CPPs only, or should noncritical parameters be included? When might the latter be appropriate? DS should include all relevant parameters required for assurance of product quality, not just CPPs. If a DS were based solely on CPPs, defining them would require a much greater level of understanding. If you include some control of non-CPPs — or include them somehow into the DS — then data requirements may be lower. If the DS includes CPPs only, then a thorough data package will be needed to convince regulators that you can ignore controls or inclusion of non-CPPs. But non-CPPs should still be controlled in a manufacturing procedure; it is how they are monitored, what their ranges are, how deviations are dealt with, and so forth that will be different. Because each company can use different risk-acceptance profiles to define criticality, it will be difficult for regulators to accept a risk assessment without in-depth review.

It is still unclear how to differentiate between a statistically significant CQA effect from a practically significant impact. That determination currently appears to be in the eye of the beholder, and a universal definition may not be possible. There is concern that the definition of *criticality* depends heavily on the operating range studied. Changes beyond that particular operating range need to be managed appropriately.

Someone commented that "DS is not defined by CPPs alone. Assurance of quality defines DS. Regardless of the risk assessment instruments, terms, or definitions you use, your DS must provide an acceptable level of assurance that it will produce safe, efficacious drug product — and that your QMS will adequately handle all movements within the DS."

Someone else mentioned that to diminish and eventually eliminate "endless negotiations" regulatory agencies, the industry must come to some common understandings of definitions, requirements, and so forth — and we are not there yet. Experience is the only way to get there, and companies willing to garner that experience are paving a road for the rest of the industry.

How should companies handle parameters that are not included in the DS? Do we apply an infinite range? Parameters not included in a DS should be controlled within the overall quality system. Examples include manufacturing parameters (MPs), process monitoring, change control assessments, risk assessments, and so forth. That's not a regulatory commitment, but those are filed in the development section. Companies must consider ranges for parameters not included in a DS. At some point, a process/parameter can be great enough to have an impact, even if it is very extreme. Such ranges may be based on limits that have been tested beyond normal operations — "knowledge space" — although justification of wider ranges may be based on prior knowledge.

After much discussion about handling non-CPPs, non-CQAs, and all things noncritical, one audience member asked whether we truly believe in our risk-assessment tools — and if so, why are we so worried about what is not critical. However, regulators are concerned about the concept of a "limitless DS" and complete lack of control for elements deemed noncritical. One commenter summed up the industry's stance: Although the QbD paradigm provides for noncritical quality attributes, nothing is left to chance. Everything is well-controlled and monitored because that's good science and common sense.

What actions should be taken if a unit operation response is not as expected either at pilot or manufacturing scale? This may mean that prior knowledge of the function or operation of a given unit and/or its impact on the product is incorrect. It depends on the stage of development at which this occurs. The earlier such a deviation occurs, the more likely its impact can be rectified easily. Late-stage failures or unexpected results may require a more comprehensive evaluation of assumptions and data on which DS (or process understanding) is based. In either case, all data relating to a unit operation should be reassessed in light of the failure. Depending on those results, other unit operations, risk assessments, or process quality attribute (PQA) assessments might need revisiting.

DS, many forum participants stressed, is an iterative process. It is bound to change as more data are collected and the knowledge space increases. It is desirable to identify necessary changes early in the process,

of course, but it is possible that situations will occur such as the failure of a unit operation at pilot or manufacturing scale. At a minimum, all data then would have to be reassessed.

How might a DS change across the life cycle of a product? What types of new information could identify a new DS limit? Knowledge gained over time during development can influence assumptions or back up existing data in modifying a DS — either expanding or contracting it. Processes nearly always undergo change, and new or altered processes can provide new data that influence the DS: e.g., comparability data, stability data, and testing at different limits/conditions. Additional manufacturing, preclinical, or clinical data could enhance product knowledge, turning CQAs into non-CQAs or vice versa. Process/product impact may become evident with more manufacturing experience at scale.

How can DS modifications be filed throughout the life cycle of a product? It depends on when the DS is initially "fixed." If changes are made between then and the license application, then those changes would be described in the marketing application (MA), biologics license application (BLA), or other filling. Should changes occur after approval, then filing them should be related to the extent and type of change (annual report, changes-being-effected, prior approval supplement, type II, or type I variations). This filing strategy can be preapproved in a protocol as part of the market authorization and built into the quality system. A common understanding is needed — in the United States and elsewhere — of what must be submitted in regards to description of the QMS and how that will influence the need to file design-space modifications.

Regulatory or Submission Impact

How should the DS be described in a submission? Your DS description must provide justification of parameter scoring from the risk assessments used to design process characterization experiments, including data on how decisions were made. It should include justification of small-scale–model qualification against large scale. The DS description applies only to the area in which a CQA is affected. You should describe the linking of individual steps across your process to ensure CQA control.

It is still unclear exactly what parameters to include in a filing (the CPP and non-CPP argument) and how much detail: Should non-CPP limits be tested?. However, we do know that process steps with DS are part of license claims with parameter ranges and mathematical models. We don't yet know whether to include graphical representations and/or data summaries. We need to ensure a balance between more data required and flexibility for change without reporting — and discern data for filing from data to be available on inspection.

Your description of manufacturing and process controls should be filed in Section 2.2. Again, there are still questions about what to include and where: CPPs, non-CPPs; CQAs, non-CQAs. What must be included in the DS description? How much detail needs to be included about input variables, process parameters, and QAs covered by DS and about input material controls and process controls? Should you include model representations, equations, and/or a combination of ranges?

Control of materials (Section 2.3) should include detailed input material controls and CQAs for starting materials. Control of critical steps and intermediates (Section 2.4) should include input controls. Development (Section 2.6) will need to include development strategy, CQA and CPP selection, QRM, prior knowledge, DoE, multi- and univariate analysis, lot and process history, and comparability. Process validation and/or evaluation (Section 2.5) should include evaluation of operating units, storage/hold times, column lifetime, compatibility, viral safety, and so forth; evaluation of DS, validation, and confirmation of consistency (in process and end product); and movement toward continuous process verification. It is unclear as to whether there should be a continuous process verification protocol, change management protocol or stability protocols. But you do need to demonstrate that your DS model is not affected by a particular change.

One person asked how regulators deal differently with a "regular BLA" compared with one based on QbD. Regulators said that they are still figuring that out. So far, they are looking very closely at QbD applications because they sometimes seem ambiguous, and regulators' level of comfort requires close scrutiny. One criterion specifically mentioned is the clarity of the CQA and CPP definitions used in a filing. ICH Q8-R2 defines both terms, and regulators are most comfortable with sponsor definitions that hold closest to those ICH definitions. However, Ron Taticek pointed out in his presentation, "It is not clear how to interpret the ICH definition of critical process parameters: A CPP is a parameter that has both a statistically significant and a practical (nontrivial) impact on the CQAs."

Regulators will also look closely at ranges and the strength of data used to support them. Are noncritical parameters still within the ranges you actually studied? If not, how can you be sure that they are still noncritical? How do you propose to handle noncritical parameters and quality attributes after approval? What do you propose to cover in your QMS, and what is reportable? Again, the consensus among regulators seems to be, "It depends. . ." Constraining CPPs would be less cause for regulatory alarm than expanding them but might still cause regulatory concern.

How can movement at the edges of a DS be justified/implemented (e.g., "adaptive" control strategy or statistically justified)? Statistical limits can be bound into a DS (e.g., statistical boundaries and CPKs) to provide a level of confidence when approaching edges of DS. When at its limits, the qualification of small-scale models (with edges defined) is even more essential. You could increase testing as you approach the DS edges

to assure product quality. Not all edges are equal; some may be a cliff, others just a gradual difference, so statistical limits can be applied as appropriate. A QMS may treat different excursions differently depending on their potential product impact. You could file a strategy describing how such excursions would be handled (more studies, based on existing knowledge, risk assessment, and so on) or how a QMS will deal with uncertainties associated with movement near the edges.

A DS system is asymmetric. A change near the middle might have greater or less effect on the resulting product than the same change near the boundaries. Although the assumption at filing is that a sponsor knows the CQAs for a given product, uncertainty remains. Could the sponsor be missing "the rest of the iceberg?" Negotiations with regulators should be expected with a QbD filing until their comfort level has increased with the process and a sponsor's ability to work within it.

QMS and Life-Cycle Implications

What is the role of a QMS in approaching critical and noncritical process parameters, especially in regard to deviations or excursions? A QMS change-management program is essential to assure both a manufacturer and regulators that changes within a DS will be dealt with appropriately and may not have to be reported (or can be reported in a reduced category). Deviations and excursions should be dealt with normally, with enhancements required to ensure adherence to a DS and/or expanded change protocols (eCPs). The effect of a deviation on a non-CPP may not require the same level of investigation as deviation to a CPP depending on the nature of the deviation (e.g., within the knowledge space). This is not too different from the current system of going within or beyond validation limits.

Deviations that require DS revision (either shrinking or expanding) may require some sort of a filing (level determined according to the type of change) to "reapprove" it or at a minimum to keep the agency informed. If a deviation reveals that a non-CPP is in fact a CPP, then the DS and other related systems (e.g., risk, small-scale model qualification) would need revising through a QMS change-control procedure.

What role does the quality system play in approaching CPPs and non-CPPs regarding planned movement within the DS or approved protocol? A QMS should be able to handle movement within an approved DS through preapproved enhancements to such systems as change control or process monitoring that ensure appropriate documentation, process control, and product monitoring to prevent shifts in process capability or product quality. Obviously the level of change management will be different for non-CPPs than for CPPs as far as how the system handles movement (level of assessment, testing data required, postchange monitoring, reportability, and so on). A non-CPP movement beyond the range that defined its criticality would require enhanced scrutiny. Perhaps a defined limit to movement within a range (e.g., 50%) would be a compromise to allowing totally free movement. Aspects of the QMS enhancements required can be filed whereas others are made available on inspection.

Forum participants brought up a number of specific testing methods and discussed their desired frequency, specificity, and other questions. ICH Q1D (*Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*) makes clear that many factors need to be taken into account when designing complex testing strategies. The information necessary for regulators to accept such approaches in designing a QbD control strategy remains unclear.

Again, the industry generally agrees that non-CPPs and non-CQAs will be controlled within a QMS. Questions remain as to what becomes part of the regulatory commitment and what does not — and thus what requires a report to the agency and what does not.

Someone pointed out that under the current paradigm, attributes such as "sterile" might be included in a license, but all the details of achieving and maintaining sterility would not be included. The intent of "sterility" is met through environmental monitoring and personnel practices as well as validation and testing. So the output (sterility) is a regulatory commitment; it doesn't describe every detail of how that is to be accomplished.

What is the role of the QMS in approaching CPPs and non-CPPs after approval? How should a system manage and document oversight of the continuous monitoring process, and how should process improvements or optimization be implemented and communicated to the agency? A QMS can be enhanced to include improved process monitoring (e.g., holistic monthly product review), statistical trending, and appropriate actions should trends be found. Such enhancements can be filed. The management of process improvement filings can be predefined as part of change control depending on the level of change; they can also be filed (e.g., as part of a change protocol). But could Section 2.2 include a commitment to update DS equations, for example, through an annual product review (APR)?

We discussed a number of questions, including what level of changes within acceptable ranges might require reporting. The guidance indicates that "nontrivial, significant, and impactful" changes should be reported, which industry considers too vague. So questions remain. One person suggested that such changes might be included in Section 2.5.

Control Strategy, Life-Cycle Management

How would control strategies look different for traditional and QbD submissions? A QbD control strategy is based on a holistic, comprehensive assessment of the criticality of quality attributes, linking that to how they affect a process and defining process controls and product testing to assure quality, safety, and efficacy. The strategy includes risk assessments, prior knowledge, and enhanced

molecule and process understanding to leverage preclinical and clinical data with testing capabilities. So in-process controls, specifications (product and raw materials), and stability programs will be based on criticality of quality attributes and probably be more streamlined, with fewer items (or fewer with high stringency) than a traditional approach.

A QbD control strategy should consider how unit operations affect product across the manufacturing process (and interactions among those operations). A QbD control strategy moves control to the process for delivering high-quality product — rather than testing quality into a product. This control strategy also includes the concepts of continuous verification (e.g., increased multivariate analysis) and continuous improvement. This is the life-cycle approach. The strategy would inevitably include more data and justification in process characterization, process control, and justification of specifications sections of a filing. A QbD control strategy also needs to deal with different levels of uncertainty for a DS.

How would parameters that are unspecified in the license be handled, and what is the agency's involvement? Unspecified parameters such as process monitoring, change control, and noncriticals should be handled by a QMS. How that system deals with those parameters (noncritical process parameters, inputs and outputs, and quality attributes) can be described in a filing or be made available on inspection.

We recommend an annual report as the best way to report such changes. One regulator asked, "If validation and DoE have been done and included in the filing, why does the agency need to see that again in an annual report?" Another stated that movement within a DS is not a change, so there is no need to communicate that to the agency. Another, however, pointed to "cascading uncertainty" at the edges and was of the opinion that changes toward those edges should be reported. According to guidelines, however, it is up to a sponsor (once its product has been approved) to decide whether and when a movement within a DS should be reported. But the agency is uncomfortable with that and will request reports when inspectors deem it necessary. So a clear and understandable guidance is still needed; so far, Q11 does not appear to be it. Someone asked whether and how it might be rewritten to provide useful guidance for both regulators and industry.

What additional considerations — beyond criticality of a given attribute — factor into control strategy development? An attribute that indicates process consistency (e.g., glycosylation) but cannot be easily measured through another parameter may need to be considered as part of process monitoring or on comparability, but not necessarily in routine lot release or stability. An attribute that provides data about the ability to supply patients (e.g., yield) would require some form of assessment (in-process).

Are the FDA's eCPs and the European Union's postapproval change management protocols (PAMPs) the same? If not, what are the key differences? Because both eCPs and PAMPs are very new, we don't yet know what their key features will be or how they will be implemented.

QbD for Other Products

What challenges would come in justifying the described immunogenicity operating space for a vaccine? In determining a vaccine's immunogenicity operating space, you need to understand how the molecular fragments and three-dimensional structure truly affect the immune system — e.g., stimulating only what we want to because we want a natural, protective immune response. That may require designing additional studies to further examine how the product works. You may need to go beyond the traditional potency assay to better characterize and predict response. Immune response is certainly a biomarker for vaccines, but it may not reflect efficacy. An understanding of patients' responses to a vaccine is also important. It seems clear that QbD can be applied to vaccines and that it is important to know how to manufacture the product and how it works. Ensuring a continuous supply for vaccines is no different than for any other product.

What studies would be needed to justify an "immunogenicity operating space" for a therapeutic protein, for which immunogenicity is undesirable? First and foremost it is necessary to understand what actually causes immunogenicity for a particular product. You can use epitope mapping of antibodies to identify where in a molecule they bind. It can also be useful to monitor which lot of material each patient gets and to control the levels of quality attributes those lots get — and take into account patient-specific responses (e.g., major histocompatibility complex contributions). You can use preclinical or nonclinical studies to understand the immunogenic potential of your product (e.g., in silico or in vivo testing). A thorough understanding of product variants and process-related impurities is necessary, and all prior knowledge could prove useful.

Several elements of QbD can be applied across multiple product types and associated systems. What essential components can be applied most generally? Some essential components include planning and design (e.g., molecule design, equipment, and facility), execution (training, clear SOPs, streamlined

processes/methods), monitoring (e.g., statistical process control and multivariant analysis), continuous improvement (e.g., corrective and preventative actions), and risk assessments. Some elements of QbD are becoming regulatory expectations. Forum participants mentioned that we have been doing "QbD light" for years (e.g., process/product interactions, criticality of in process controls) and that CGMP is an expectation (better justification for reassessment of specifications and in-process controls, risk assessments, good science, and common sense).

What elements of QbD appear to be the most difficult, costly, and/or time consuming? Forum participants mentioned DoE, data accumulation, and reporting of DS as potential barriers. Multiple risk assessments are clearly time-consuming. Another barrier is developing extensive eCPs rather than one-off comparability protocols. Because QbD is not globally accepted, using it can lead to different filings in different jurisdictions, which can be both costly and time consuming. However, QbD is still worthwhile. Many aspects of it are very cost effective — molecular design and CQA understanding, for example — and can be applied by companies regardless of size, product, or process.

How are companies making decisions over how much (if any) QbD will be applied to a particular product, especially considering early phase, late-phase, and licensed products? For reasons such as attrition of molecules through development and the cost and time to carry out specific aspects of QbD, it may not be financially viable to apply to all molecules. We need to establish a strategic framework to guide the circumstances in which to apply QbD. Such a framework might include probability of success based on knowledge of the biological pathway, availability of clinical data, and market position. It might also include process/product complexity, taking into account whether or not you are working with a platform, whether your drug product is lyophilized or liquid, whether you are working with an established or a new technology, and specific regulatory risks including patient population and indication. The framework might also include material demand: Will treatment be chronic or acute, high or low potency, and does it involve high or low plant use?

Global acceptance of QbD by regulators is one barrier to holistic implementation. How are companies managing global filings? The two options expressed at the forum were essentially producing two different files or "file all data and wait for questions."

What are the main concerns companies have in implementing QbD? Although it certainly benefits molecular design and process development, companies worry about QbD's effect on time and expense of developing products. They wonder whether QbD will really allow for more rapid development if platform knowledge is applied. Some people are concerned that questions from regulators will increase as more data are provided in filings. Companies wonder whether the cost and time of QbD will be recognized from a cost of goods perspective as opposed to a better process and product understanding. Will QbD have inherent value to the industry? Does it actually prevent multiple failures that might occur under the traditional approach? Are QbD-based products of better quality than before? Concern continues to be focused around DS, efforts to create it, and what regulatory and/or QMS relief will come (if any).

Apart from process and product, on what other applications can QbD have an impact? The answers to this question include equipment design, implementation, and execution; facility design and utilities; raw materials; containers; transport; and QMSs.

Advancing with Caution

Although many questions remain, collaborations between the FDA and industry are bringing QbD ever closer to realizing the potential of building quality into biopharmaceutical products rather than controlling it after development. Many early questions — such as defining CQPs, CPPs, and DS — are beginning to get answered. The answers are becoming more consistent across projects and companies. Plenty of work remains to be done, but our progress is clear and inspiring.

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