THE QUALITY REGULATORY INITIATIVES UNDERWAY AS THE NEW DECADE BEGINS

show the strong imprint of ICH Q8-10 at both the agency and international levels.

From CMC application review to GMP inspections, from development to post-market manufacturing, from the ingredient supply chain through product distribution, the quality-by-design, risk management and quality system principles built into the new ICH guidelines are being integrated into industry/regulator interactions and the guidance, policies and initiatives that define them. As experience with ICH Q8-10 implementation grows, the knowledge gaps that need to be filled are coming into sharper relief, and industry, regulators and academia are in close dialogue on how to fill them. Managing and regulating the flow of quality-by-design knowledge from development into manufacturing and through the production lifecycle are central challenges on the table. The value of the QbD building blocks is becoming better understood while questions are emerging on how that value can best be realized and with what regulatory implications. The lifecycle interdependence of the Q8-10/QbD components is leading regulators to rethink the way their review and inspection organizations have interacted.

EDITOR’S NOTE: This issue of IPQ analyzes the impact the new QbD paradigm is having on the initiatives and dialogue around reshaping the CMC review process. In the next IPQ issue (June), the focus will shift onto how the inspection and GMP enforcement components of the regulatory picture are being impacted as the quality system foundation for continuous improvement strengthens.

VOICES FROM THE DIALOGUE:

• CDER’s Christine Moore on implementing QbD for drugs (Appendix I, pp. 42-45)
• CDER’s Steven Kozlowski on implementing QbD for biotech products (Appendix II, pp. 46-48)
• EMA’s Evdokia Korakianiti on the implementation of QbD in Europe (Appendix III, pp. 49-53)
• CDER’s Nakissa Sadrieh on regulating nanotechnology in therapeutics (Appendix IV, pp. 54-61)
• Genentech’s Christa Hartmann on a new knowledge management paradigm (Appendix V, pp. 62-64)

TABLE OF CONTENTS:

ICH
ICH Focusing On Q8-10 Implementation ............... .3
Drug Substances, Methods Also On ICH Screen ....... 5
ICH Takes On Heavy Metals ............................ 5
Cultural Change Takes Time And Effort ......... 6

FDA & EMA
CDER QbD Experience Expanding .............. .9
The Gaps That Need Filling .........................12
Continuous Manufacturing Touted by FDA .......13
Biotech QbD Pilot Focuses On Clinical Relevance ...14
CDER MAPPs Out Biotech Reviewer/Inspector Roles .15
FDA Generic Drug Review – Through QbR to QbD ....17
ICH Vision Taking Shape In EU With PAT Team Help ..19
Workshops, New Guidelines Support EMA Efforts ....21

Ireland Following Suit With Industry Collaboration . . .23
FDA, EMA Work On Clearing CMC Change Pathway . . .24

THE ISSUES
Risk Management – What’s The Score? ...............25
Design Space Still Contains Some Rough Edges ....26
QbD Puts Spotlight On Knowledge Management ....28
The Burden Of Knowledge ............................29
Models Help Development And Submissions ........30
QbD For Analytical Methods Having Strong Impact ....32
Application of QbD In Analytics Poses Some Issues ....33

OTHER ORGANIZATIONS
NIST Offers Help In Biotech Measurement Standards .34
USP, PQRI Exploring Their Roles .......................36
QbD Gaining Traction In Non-ICH Countries ..........40
The pharmaceutical quality regulatory initiatives underway at both the agency and international levels as the new decade begins show the strong imprint of the quality by design (QbD), risk management and quality system principles embedded in the ICH Q8-10 guidelines.

The regulatory impact of the new ICH Q8-10 paradigm stretches from marketing application review to GMP inspections, from drug development to post-market manufacturing, from product to process analytics, from the ingredient supply chain through product distribution, and from the three ICH regions to regulators worldwide.

Regulators, manufacturers, contractors, suppliers, consultants, lawyers, academics and their associations and related standard-setting organizations are all being drawn into the effort to comprehend the full meaning and potential of the paradigm shift and to figure out how the evolving principles can and should be implemented.

Communication boundaries are expanding and new ways of working together explored to help address the challenges involved.

Companies are breaking down their internal barriers to interdepartmental communication as they seek to upgrade their knowledge management processes and information flow to keep pace with the changing environment. The boundaries within agencies are also breaking down as the review and inspection components align to a QbD/lifecycle-management regulatory approach. Similarly, communication barriers between industry and regulators and between agencies internationally are coming down and new communication and cooperation channels formed.

The next decade will be one of rapid change as the emerging initiatives reshape the regulatory landscape.

Globalization of the supply, production and distribution chains, product and process changes driven by a fast-moving technology, and increasing budgetary and resource pressures at both the producer and regulator levels are forces driving the transformation. These forces have compounded the need for marshaling together the available expertise in the effort to implement a coherent, harmonized regulatory philosophy that can provide a solid foundation for addressing the complex issues involved.

As a locus for regulator/industry dialogue, ICH continues to play a key role in shoring up this foundation and providing QA oversight on a harmonized Q8-10 implementation process.

Reviewing FDA’s quality regulatory initiatives for a predominantly European audience at the APIC/CEFIC annual meeting in Venice in November, Center for Drug Evaluation and Research (CDER) Office of New Drug Quality Assessment (ONDQA) Director Moheb Nasr pointed to the growing influence of the ICH guidelines, and Q8-10 in particular. As head of the CMC review process in the U.S., Nasr has been playing a pivotal role in FDA’s implementation efforts and serves on the ICH Q8-10 Implementation Working Group (IWG).

An extended timeline of FDA guidance development clearly illustrates the shift, he said. “Ten years ago, we were relying mostly on U.S. FDA-developed guidelines. In the last five to ten years, we have been working under ICH and relying more on international collaboration and harmonization for our quality guidelines.”

Nasr highlighted the key development, risk management and quality system principles embedded in ICH Q8-10 and emphasized the lifecycle/continual improvement nature of the paradigm through which the three facets interlink.
The development facet described in Q8, Nasr explained, encompasses a quality-by-design (QbD) approach involving the determination of the quality product profile and critical quality attributes (CQAs). Raw material attributes and process parameters are linked to the CQAs and risk assessments performed, and a design space developed. A control strategy then needs to be designed, implemented and managed through the product lifecycle, with continual improvement to the QbD structure.

The systematic process for the assessment, control, communication and review of quality risks described in Q9 also extends over the product lifecycle – including development, manufacturing and distribution. Q9 includes principles and examples of tools for this quality risk management.

In turn, Q10 describes the systems for establishing and maintaining the state of control for process performance and product quality. Again, Q10 applies to both the drug substance and drug product throughout the product lifecycle, with the goal of facilitating continual improvement.

The power of the ICH Q8-10 guidelines, Nasr suggested, is not the newness of the principles, but that they are more clearly defined and a systematic process for implementing them provided – improving communication within companies, between companies and regulators, and between agencies internationally.

For example, Q8 really does not define “a new way of developing pharmaceuticals,” the ONDQA director commented, but provides a more systematic approach “to develop and to share the information when you register new products.”

Similarly, the quality assurance principles embedded in Q10 have “always been important.” However, the regulatory flexibility that manufacturers seek for both API and drug product manufacturing “requires effective change management [which] is better developed if you have a robust quality system” as outlined in Q10.

At both the ICH and regional levels, the Q8-10 implementation process continues to expand in depth and breadth, and the speed at which this process is unfolding is increasing.

There is a growing realization that the only real limit to regulatory change is the knowledge base and communication needed to bring it about.

The agencies, as market gatekeepers, are fully empowered to require what they deem necessary to assure the quality of products through their lifecycle and to raise the bar as science and technology create better solutions.

Reviewers are constrained not by regulations per se but by their mission of serving the public health, wherein setting the quality bar too high may be counterproductive. Investigators, in turn, are empowered to make sure that application commitments are adhered to. As such, they can also be full participants in the paradigm change without an overhaul to the GMP statutes.

Increasingly aware of this opportunity for regulatory transformation, industry, regulators and academia are stepping up together to the challenge of defining and filling the knowledge gaps.

From risk assessment to design space to the use of models to knowledge management to PAT applications to continuous improvement, the QbD links are coming together to form a more coherent development, submission and post-market manufacturing regulatory chain.

The Q8-10 implementation initiatives have, in turn, helped bring into relief the key questions that remain to be addressed. The international regulatory community is working closely together in a variety of forums to formulate viable answers for all involved.

ICH Focusing On Q8-10 Implementation

Recognizing the high level nature of the Q8-10 guidelines and their conceptual sophistication, ICH formed its “Implementation Working Group” (IWG) in mid-2008 to help assure that there is clear understanding of the principles they contain and a harmonized interpretation.

Discussing the IWG role at the APIC conference, working group member Nasr explained that ICH has been good at the development of harmonized guidelines. “What it has not been as good at,” he commented, is making sure the implementation of these guidelines within and outside the ICH regions is harmonized – that “once they leave the room where the experts got together to develop these guidelines, everyone had a clear understanding and implemented consistently.”

As part of its mission to help with this objective, the IWG has been developing Q&A documents intended to clarify the more significant interpretation issues that have surfaced.
A first set of Q&As was cleared for ICH website inclusion in April 2009, with a second set added following the October 2009 ICH meeting in St. Louis. Additional Q&As are being worked on for clearance by the ICH Steering Committee. The IWG continues to welcome questions and comments, which will be discussed by the working group at its following session for potential inclusion on the website.

To date, 46 Q&As have been published. They are grouped into topic areas, including general clarification (3), quality by design (26), quality system (8), GMP inspection practice (3), knowledge management (5), and software solution (1). The 26 QbD-related Q&As include eight on design space, 12 on real time release and five on control strategy. Most of the questions the IWG is currently working on also relate to QbD, including eight more on real time release and three on design space.

A second focus of the ICH IWG is on developing case studies through collaboration with outside organizations and technical experts to show how the concepts for development and manufacturing of APIs and dosage forms can be put into practice.

The IWG has identified about 20 proposals for consideration. Of these, three have been judged highest priority and the IWG has begun work on them. The three topics involve life-cycle knowledge management, scale-up considerations in manufacturing, and the handling of a site change.

A third prong of the IWG program is to hold “practical” training workshops in each of the three regions.

The workshops, open to the public, including regulators and industry, will cover the integrated implementation of ICH Q8-10 across the product lifecycle, including pharmaceutical development, manufacturing, regulatory assessment, scale-up to commercial operation, and GMP inspection.

The preliminary agenda calls for the training to last two days. The first half day consists of plenary sessions, followed by a full day of small training breakouts on design space, quality risk management, the control strategy and the quality system, concluding with a half day of workshop conclusions and “next steps.”

The faculty will be regulator and industry experts either on the IWG or involved in the development of the ICH Q8-10 guidelines. Information from the workshops will be used by the IWG to support the harmonized implementation of ICH Q8-10, with the workshop materials designed to be suitable for internal training by industry and regulators.

The first of the training workshops will be held in Tallinn, Estonia in early June immediately preceding the regular ICH meeting there. The U.S. workshop will follow in October in Washington, D.C. The Japan training will be held in November in Tokyo, again in conjunction with the previously scheduled ICH meeting there. The European and U.S. trainings will be cosponsored by ISPE and PDA on behalf of ICH.

Nasr views the practical implementation thrust of ICH as “one of the most exciting things that we have worked on in the last few years” in evolving the ICH quality paradigm, “because in my estimate, that is really what was missing.” The goal, he explained at the APIC conference, is to present different ways to implement the high level guideline concepts “not only in the development at the bench, but when you implement at full scale,” along with “the views of the regulators and how the regulatory assessment and inspection will take place.”

Another key component in the ICH implementation effort is its Global Cooperation Group (GCG), which is focused on extending the impact of the guidelines and ICH’s harmonization goals beyond the US, Europe and Japan.

The GCG brings participants together to engage in the ICH process and organizes discussion forums and training and other regulatory implementation initiatives globally, regionally and nationally.

The GCG includes representatives from each of the six parties on the ICH steering committee as well as from ICH observers – the World Health Organization (WHO), Canada and the European Free Trade Association (EFTA). Also included are representatives from “regional harmonization initiatives” (RHIs) and from individual regulatory authorities.

Participating RHIs are the: Asia-Pacific Economic Cooperation (APEC), Association of Southeast Asian Nations (ASEAN), Gulf Cooperation Countries (GCC), Pan American Network on Drug Regulatory Harmonization (PANDRH) and Southern African Development Community (SADC). Countries invited to participate include: Australia, Brazil, China, Chinese Taipei, India, Singapore and South Korea.
The scope of activities as defined in the GCP mission statement is a substantial one – “to promote a mutual understanding of regional harmonization initiatives in order to facilitate the harmonization process related to ICH guidelines regionally and globally, and to facilitate the capacity of drug regulatory authorities to utilize them.” The ICH website (ich.org) includes a GCG component which details its membership, objectives, meeting calendar, and current activities.

**Drug Substances, Methods Also On ICH Screen**

Another current thrust of ICH in the quality arena is the development of a guideline to accompany the ICH Q8-10 series focused specifically on drug substances.

The objective of the “Q11” guideline is defined as harmonizing the scientific and technical principles relating to the description and justification of the API design, development and manufacturing process.

Q11 will address the concepts embedded in ICH Q8(R) – for example, related to development, the use of quality risk management, quality by design and design space – as they apply in the drug substance context. In addressing the manufacturing/validation aspects, an effort will be made not to create redundancy to the ICH drug substance GMP guideline Q7A. Q11 will be applicable to both small molecule and biotech APIs.

The ICH steering committee approved the concept in April 2008 and the Q11 Expert Working Group (EWG) held its first meeting in June 2008. The EWG has worked through a few preliminary drafts based on the concept paper and is hoping to have a “Step 2” document cleared for public comment at the ICH meeting in Estonia in June.

The draft from this Fall includes an introduction and glossary, and sections on: manufacturing process development (CTD section S 2.6); definition of starting materials; manufacturing description; controls; and process validation/evaluation.

Asked at the APIC meeting if the Q11 guideline would provide specific examples since Q8 did not contain them for APIs, Nasr responded that he did not anticipate a focus on them in Q11. “The problem with giving specific examples,” he explained, “is that some people may use them as a template – that all future development and manufacturing has to be done the same way as the example.”

The upcoming ICH workshops, Nasr said, would help fill in the gap – for instance, by addressing examples on different approaches to developing the design space for an API process and how it will be evaluated by regulators. The examples will consider “the type and level of detail of information needed, how such a design space will be implemented at the manufacturing facility within a quality system, and how the inspection should be conducted in looking at the design space.”

Another current focus of ICH attention in the quality area is the ongoing effort to harmonize pharmacopeial texts in the three regions to reduce redundant or unnecessary testing requirements. **Substantial progress was made on this front at the St. Louis meeting.**

Three more annexes to the Q4B guideline achieved final “Step 4” clearance for publishing in the US, European and Japanese Pharmacopeias: **Annex 7** on dissolution, **Annex 9** on tablet friability and **Annex 10** on polyacrylamide gel electrophoresis. Drafts of another two reached Step 2: Annex 11 on capillary electrophoresis and Annex 12 on analytical sieving.

The clearance process basically involves the Q4B EWG working through the Pharmacopeial Discussion Group (PDG) to assess the general method chapters in the regional pharmacopeias, outline issues that need consideration and address them. The respective Q4B annex is then developed, which recognizes the analytical procedures as interchangeable, subject to the particular conditions outlined. The annexes also contain a section on “considerations for implementation” that addresses the impact of the different regulatory mechanisms in the U.S., EU and Japan.

Thus, the ICH process is helpful not only in reducing testing complexity and redundancy through general chapter harmonization and the allowance for interchangeability, but in clarifying how the testing requirements and their enforcement vary in the three regions.

**ICH Takes On Heavy Metals**

Also receiving attention at the St. Louis meeting was a proposal for extending the Q3A guideline series on impurities to address heavy metals under the moniker “Q3D.”

Reflecting the concerns of the regulatory community regarding heavy metals and the desirability of a harmonized approach to the criteria and methodologies needed to control them ([IPQ, Nov./Dec. 2008, pp. 37-39](IPQ)), the ICH Steering Committee endorsed the proposed plan and the setting up of a Q3D working group. This EWG will include chemists with backgrounds in QA and R&D along with toxicologists.
The guideline will be similar in form to the other guidelines in the Q3 series, which cover impurities in new drug substances (Q3A(R2)) and in new drug products (Q3B(R2), and residual solvents (Q3C(R4)).

The concept paper on the Q3D initiative, submitted to the steering committee in July for consideration, makes a compelling case for the need and value of “a harmonized guidance to help assure the appropriate control of metal impurities in drug products and ingredients.”

The proposal explains the current lack of harmonized guidance in this area at the agency and pharmacopeial levels. The problem with pursuing the concern through the Pharmacopeial Discussion Group route is that the analytical procedures and acceptance criteria for inorganic impurities in need of updating are contained in both general chapters and specific monographs for excipients, drug substances and drug products, and the later monographs are not in the PDG’s scope.

In turn, “the challenges associated with non-harmonized pharmacopeial standards for inorganic impurities are exacerbated when consideration is given to the lack of harmonized regulatory guidance in this area,” the paper points out. EMA has recently provided guidance on specification limits for residues of metal catalysts and reagents, but similar guidance has not yet been provided by the US or Japan. Also, the paper points out, the EMA guidance does not address several metals posing significant toxicological concerns, in particular lead, mercury, arsenic and cadmium.

Recognizing the work USP has been doing to upgrade heavy metals testing standards and the EMA guidance, the paper expresses concern with the possible divergence in approach and acceptance criteria between the pharmacopeias and regulatory agencies.

“A harmonized ICH guideline to address inorganic impurities, and specifically metal impurities, will help ensure appropriate control for these impurities, to the benefit of public health,” the Q3D proposal states. “The ICH guideline will ensure that new requirements have the necessary input of the regional regulatory authorities to help protect patient safety, and should also help to avoid differing approaches and standards among the pharmacopeias and regulators. This consistency will avoid current redundant testing to meet different requirements, and will make the implementation of the harmonized outcomes more readily achievable by the pharmaceutical industry.”

According to the plan, Q3D will provide a risk-based approach to ensure control for metals likely to be present in drug products and ingredients, “including those resulting from the manufacturing process (metal catalysts and reagents), as well as those due to the material source (e.g. Pb, Hg, As, Cd).”

The plan further explains that the new guideline will focus on establishing appropriate limits for specific metals rather than the details on the analytical procedures to be used. “Harmonized analytical procedures should be established by the pharmacopeias for determining levels of metal impurities, with allowance for use of any appropriate validated procedure for a particular application.”

The ICH project will piggyback off the EMA guideline, which was structured similarly to ICH Q3C on residual solvents, thus shortening its projected development timeline to between one and two years from work initiation.

Cultural Change Takes Time And Effort

While enthusiastic about the implementation outreach that ICH is doing, IWG members also caution that time and effort will be needed to allow the full potential of the new paradigm to unfold – particularly in terms of building a more flexible and efficient quality regulatory process around the expanding QbD knowledge base.
Pfizer Quality Strategy VP Georges France, who represents EFPIA on the IWG, refers to “the need to be realistic” in his presentations on the ICH implementation process.

The first step of the process is the internal investment by companies in better understanding of development and process robustness, which has an immediate payback in increased efficiency/yield and the reduction in out-of-specification, recall and supply chain problems. A second step in ICH Q8-10 implementation is the training and piloting effort currently underway. In the third step, trust and harmonization have been achieved, allowing for the full benefits of regulatory flexibility, decreased inspections, innovation and continuous improvement, and post-approval changes to be realized.

The current training and piloting stage is “critical,” France commented at the Product Quality Lifecycle Implementation (PQLI) track at ISPE’s annual meeting in San Diego in November, because without creating the needed understanding, the result may be “a more complex regulatory environment without the benefit – which is not a good thing in my view.”

What is needed in the current implementation stage over the next couple of years, he stressed, is “constant dialogue and sharing of experiences…to make sure that everybody is on the same page.”

The main challenge at this juncture is a cultural one, he said, adding that changing the culture will involve “learning by doing, with support from the management, with a good dialogue between regulators and industry…. Learning together is something that is very important, and training is required. It is not the theory alone which is important – it is going through practical examples and case studies.”

France also emphasized the cultural challenge at the PDA/EMA conference in Berlin a few weeks earlier. He commented that ICH Q8-10 implementation may not qualify as a “revolution,” but it does involve a “serious transformation of the processes.”

From an organization perspective, he said, a “very important step” is building a bridge between the development and manufacturing organizations. “The silo which is in most of the organizations needs to be broken to make something efficient.” And the cultural challenge is shared by the regulatory agencies: “The partnership between an assessor and an inspector and the common role between them is also a challenge in terms of the cultural aspect.”

Like all cultural changes, France continued, “it cannot happen in one day, and this is something we need to keep in mind in my view.” For practical success, the science behind QbD needs to be readable and based on robust data. “When you do QbD you need to make it understandable” both inside the company and for regulators, and clearly demonstrate “that what you are doing is based on robust data.”

He cited a supporting comment on the importance of this transparency by fellow IWG member Jean-Louis Robert, who chairs EMA’s Quality Working Party, at a joint EMA/EFPIA “QbD application workshop” held in late September in London. Robert advised that an introduction in the application filing explaining the rationale behind the development and overall control strategy for a particular product “is highly welcome.” When you have a new approach, France added, “it is very important that between [the company], the assessor and the inspector, there is good understanding” where the company wants to go.

Pfizer Global R&D Executive Director Robert Baum picked up on this theme at a QbD/PAT regulatory workshop held in conjunction with the IFPAC annual conference in Baltimore, MD, in early February.

Baum has been engaged as a PhRMA representative in the ICH quality guideline development process since its inception, serving most recently on the ICH Q8 working group, and has helped guide ISPE’s Product Quality Lifecycle Implementation (PQLI) initiative intended to contribute to the Q8-10 implementation effort.

He opened his remarks, which were designated to cover the “industry perspective” on QbD implementation, by offering insight on the way the industry/regulator perspectives have melded in the face of the implementation challenges. This melding is a significant component of the cultural “transformation” identified by France.

Those involved with the ICH implementation process “start sharing so much information that it is very hard just to see things from a certain perspective,” the Pfizer official explained. “Those of us from the industry side and regulators as well see things from a wider perspective that involves all of the stakeholders.”

Nor is the perspective stationary, Baum added. “There is so much to learn from all of this that whatever you are hearing from all of us today is probably where we are at this particular snapshot in time. Things are evolving. I think all of us who have
been involved in this would have to say that on probably many of these related issues that we are talking about, our views have changed over time, and they will change over time.”

In facing the challenges and opportunities in Q8-10 implementation, Baum stressed, “we are all in this together.”

The technologies involved, such as chemometrics, engineering, and the use and maintenance of predictive models, are relatively new to the pharmaceutical industry, and all parties, including industry and agency assessors and field investigators, “need to have a better understanding. Maybe we don’t all need to know things to the same level, but we all need to have a better understanding of what we are talking about.”

The guidelines alone are not enough, Baum continued. “A lot of the guidelines being developed are high level, and that is more or less by design. Things are evolving, and we don’t want the guidelines to limit some of the capabilities or innovation that companies have. But because of this high level, ongoing clarifications are needed with regard to regulatory expectations. We do have a moving target here.”

Baum also echoed France on the initial objective/business case for doing QbD. “I think that what we are primarily finding out today is that the objective is to develop enhanced process and product understanding, with the results being smoother transfers between R&D and manufacturing. And overall we are seeing a greater assurance of product quality.”

Regulatory flexibility is involved, he explained, “but it is usually an outcome of what we have learned about the product and the associated development and manufacturing processes. Certainly I think we are finding that there are fewer manufacturing failures that in the past may have led to product recalls.”

Baum added an insightful analysis of the progression in the use of process analytical technology (PAT) in particular.

In general, he pointed out, “there are a lot more ways now to justify PAT” as a tool for process control and for shifting the control further upstream. Employing PAT to monitor a process is the first step in the progression, which probably does not have regulatory implications. “Employing the technology to allow you to take measurements to adjust a process, to refine and optimize conditions” is the next step and does have regulatory import. “If you are using PAT where you can work further upstream and you can start learning more about the impact of your starting materials or other input variables, that is even better.”

From the technology standpoint, Baum pointed out that there is room for improvement in the variability and robustness of PAT measurements. Work also needs to be done on how to handle the large sample sizes involved. Baum explained that the IWG is encouraging the work being done by the European Directorate for the Quality of Medicines (EDQM) which oversees the European Pharmacopoeia (EP), “so we can generate a global system criteria in sampling plans for these large sample sizes.”

QBD MISPERCEPTIONS AND MYTHS

At the IFPAC conference, Pfizer Global R&D Executive Director Robert Baum remarked on common “misperceptions and myths” regarding quality by design and its implementation.

- QbD = PAT, or QbD = design space, or QbD = DOE: There are a lot of interrelationships there, but that general statement is not true.

- QbD is becoming a regulatory expectation: Well, it might be sometime, but today it is not. It is an optional development approach.

- QbD requires a design space: No, it does not.

- Cannot do QbD without PAT: Sure you can. And in fact, I would say you can do QbD without having a design space at all. In terms of PAT and QbD together, you can probably do those without any regulatory implications at all. If you want to take advantage of some of the opportunities that are there based upon what you have learned and what you understand by employing some of these approaches, then yes, there would be some regulatory implications.

- QbD is an objective to gain regulatory flexibility: There are a lot of us that probably thought that was a major reason why we might want to do this early on. I think that is becoming less and less of a general consensus view.

- The cost of implementing PAT is difficult to justify: I think for those companies that have QbD imbedded as a development approach, we are finding that is not the case.
In general, Baum maintained that the better understanding and alignment between regulators and industry needs to extend globally for a global industry to reap the full QbD benefits.

“It is a global industry these days. If we get a benefit or flexibility or an approach that is accepted in one region and not in another, we may not be much better off,” he said.

Expanding on the global harmonization needs, Baum pointed out that industry currently is dealing with the need for filing different dossiers. This regional review may result in different specifications and different interpretation of issues such as design space and real time release testing “that we have to address.”

Globally consistent implementation through IWG “hopefully will minimize some of these issues, but I doubt, seriously, if they will eliminate all of them. And then, we have the rest of the world we need to work with sometimes, as well.” The recognition of the problem has led ICH through its Global Cooperation Group to focus increasing attention on outside regions as part of the Q8-10 implementation effort.

The overall goal, as ICH has framed it, is “the new lifecycle approach to quality,” Baum stressed.

The objective “isn’t a matter of ‘this is what industry is now doing, how are the regulators going to react?’ I don’t think it works that way anymore. We are all in this together. We are looking at a paradigm, an overall quality system, that we are all stakeholders in. We are trying to look at science and risk-based approaches to product development in manufacturing and how we submit the dossier, but also science and risk-based approaches to review and inspection, and post-approval changes as well.”

“We want to get to the point where manufacturers are empowered and accountable to effect continual improvement, and not be limited in their ability to take on technical innovations, and again, this is something that goes throughout the product lifecycle. We realize there has to be regulatory oversight that is consistent and efficient, and goes across the regions.”

Baum put a sense of urgency on the ICH mission, echoing France in taking exception with FDA management’s depiction of the process at past conferences as an “evolution” rather than a “revolution” (IPQ, Sept./Oct. 2008, p. 3)

“I agree it is not a revolution, but I don’t think it is an evolution either,” Baum commented. “I think if it is evolving it is going to take too long for us to get there. There are a lot of us Type A personalities involved in this, and we want it tomorrow. We realize it is not going to happen tomorrow, but there has to be some kind of a transformation. We have to have some leaps of faith involved in this process.”

**QUESTIONS IN ICH Q8-10 IMPLEMENTATION**

Pfizer’s Robert Baum concluded his remarks at the IFPAC QbD/PAT regulatory forum by posing some compelling questions revolving around the ICH Q8-10 implementation effort:

- There are a number of firms that have embraced QbD and PAT, but why aren’t there more? Why are people sitting on the sidelines?
- If ‘big pharma’ utilizes quality-by-design principles and generic firms do not, will there be greater divergence of approval standards over time?
- Should QbD continue to be optional or should we raise the bar?
- If the business case focus is primarily on greater understanding of product and process, what is the necessity to include PAT and quality-by-design information in the application?
- Is there a risk that the new technology and the potentially large volume of data will place too many challenges on the regulators in our current environment?

**CDER QbD Experience Expanding**

FDA’s commitment to revamping its quality regulatory process to keep pace with and encourage the advancing science, technology and quality management concepts was marked by the creation of the Office of Pharmaceutical Science (OPS) in the 1990s.

OPS provides an umbrella organization over the CMC review activities in CDER. It includes the Office of New Drug Quality Assessment (ONDQA), the Office of Biotechnology Products (OBP), and the Office of Generic Drugs (OGD), along with the supporting Office of Testing and Research (OTR). Helen Winkle currently directs OPS and Keith Webber is its deputy director.
The office was set up to help harmonize and advance the formulation and manufacture of drugs along with the applicable review policies at FDA. The office’s mission includes engaging in and supporting scientific research that contributes to standard setting and technology development impacting application review. OPS liaises with USP and other organizations on drug approval standards and applicable policies, regulations and best practices.

FDA’s 21st Century drug quality initiative and its supporting guidance are an outgrowth of the OPS mission to evolve the regulatory paradigm in cooperation with CDER’s compliance office and field inspection organization. PAT, quality systems, and most recently process validation have been among the guidance focal points. The ICH Q8-10 guidelines, in turn, have built on the FDA efforts.

**OPS is currently also working on improving its own internal quality systems to help drive the new paradigm forward.**

The office took significant steps in 2009 to strengthen its infrastructure and processes. A “Quality Management System” is being implemented which will assess and improve organizational planning, CMC review, and work practices.

Each office in OPS has developed a “Quality Management Plan,” which contains short and long term goals for quality system implementation. The effort will involve evaluating the gaps and developing ways to improve work processes. Improving OPS’ CMC review quality system is expected to help in implementing QbD and providing more consistent approaches between the review offices.

OPS has participated in CDER’s rapid expansion in staffing. CDER has grown from 2,000 to 3,000 over the past few years, adding 800 in 2008 alone. In turn, there has been about a 25% growth in OPS reviewers and researchers since 2005.

This rapid increase has created training challenges. However, OPS management notes that many of the new reviewers have prior experience in the pharmaceutical industry and widen the range of expertise at CDER, which will help in reviewing the more technical information the center will be receiving in QbD-related submissions.

Each of the reviewing divisions in OPS has their own QbD implementation program tailored to the different types of products they review.

ONDQA initiated a small molecule pilot program in July 2005 to gain experience in how best to incorporate and assess QbD concepts in the CMC sections of NDAs.

Over the next year, nine original applications and two supplements were accepted into the pilot. One of the supplements ended up being split into two parts. Eleven of the applications were approved and one withdrawn for non-CMC reasons. ONDQA is currently preparing a white paper to document and share the learnings from the pilot.

**Discussing the “progress and challenges” in her office’s implementation of QbD at the QbD/PAT regulatory workshop preceding the IFPAC 2010 conference (see Appendix I), ONDQA Acting Deputy Director Christine Moore provided general insights on the pilot experience.**

The experience was important “both to the agency and to the industry about what it means to implement quality by design,” Moore affirmed. Light was shed on how to incorporate the QbD elements into submissions, such as “risk assessment, design spaces, and proposals for regulatory flexibility based upon that enhanced science understanding.” This understanding, in turn, enabled the agency to make risk-based decisions.

Moore stressed that the learnings were incorporated into ICH’s Q8(R) guideline and the steps it outlines for putting together a QbD submission.

**WHAT ONDQA SAW IN PILOT APPLICATIONS**

At the ISPE annual meeting, ONDQA official Elaine Morefield cited the following as among the “wide variety” of design spaces and control strategies provided in the applications submitted to ONDQA under its CMC QbD pilot:

**Design spaces proposed:**
- Most included drug product, some included drug substance
- Most included process parameters, some included formulation components
- Developed using varied experimental techniques & mathematical models
- Several utilized risk assessment in development

**Control strategies utilized:**
- On-line analyzers
- In-process testing in lieu of end-product tests
- Real-time release testing using PAT
Along with a better understanding of the quality-by-design building blocks, the pilot offered more general insight into the lifecycle/continuous improvement nature of the QbD endeavor and the broad development, risk management and quality system foundation on which product quality rests. The way these three factors need to work “hand-in-hand” was an unexpected revelation from the pilot experience, Moore stressed, extending its value beyond the information it provided on the application process.

Since the conclusion of the pilot, the number of QbD meetings and applications at ONDQA has been growing.

A count by Moore of applications with QbD elements in them that have come in outside the pilot in 2008 and 2009 found 12 NDAs, 18 INDs, and six supplements for legacy products addressing either new or expanded QbD elements. She notes that the number of applications that her office has seen outside of the pilot now exceeds those that were in the pilot, and she expects “this number to keep growing.”

As applications expand, so also do the challenges that industry is presenting, the ONDQA official said. The concepts and approaches are continuing to evolve resulting in “some fairly challenging regulatory approaches that the agency has not yet thought through.” However, she noted, reviewer experience is growing and the review approaches are beginning to “coalesce.”

Design space for material attributes and process parameters are among the issues that have generated discussion relating to regulatory flexibility.

One that is still developing, Moore noted, is real-time release testing approaches – “things such as in-process tests in lieu of end-product tests, and surrogate models for dissolution testing, where instead of doing dissolution tests for every batch, you are using a combination of process parameters and material attributes, or process performance criteria, to link to what that measured value would be.” Design space for analytical methods is also of interest to industry and generating discussion.

---

**ONDQA’S NASR ON LINKING QUALITY TO THE CLINIC**

At the November APIC conference in Venice, ONDQA Director Moheb Nasr highlighted the challenge of understanding the linkage between quality, safety and efficacy in advancing QbD and cited key gaps remaining for complex molecules and dosage forms.

The idea of quality by design is to make sure that the product that is being manufactured and the manufacturing process that is being used to make the product will provide assurance of quality, safety and efficacy. Because at the end of the day, that is what the patient needs. So we have been working very hard to make sure that we use better science and better approaches to assure the quality of the product…in order for the patient to receive high quality medicine.

The challenge we have had and continue to have is…the real understanding of the linkage between quality, safety and efficacy [IPQ, Sept./Oct 2007]. In some cases, we have some understanding. In many cases, we do not. So we have been focusing more on a better way to establish the critical quality attributes and the specifications based on relevance to safety and efficacy. The clinical outcome becomes very important, and that should determine what the critical quality attributes are.

Some may say, what is the difference between this and what we have been doing all along? What we have been doing all along is a checklist approach. It is a list of who made the requirements and making sure that these tests are being conducted using compendial tests. Nothing wrong with that, but the question is, how relevant are all these tests and all these attributes to the clinical outcome? A simple way [forward] we are starting to focus more on is how we can better use IVIVC and biopharmaceutics in drug development and also in our regulatory decisions.

I will give you a simple example here: In the past, the biopharmaceutics evaluation for the formulation and also clinical pharmacology was done [separately], whereas in my group we focused on the quality aspect of chemistry, manufacturing and control. There has been very good cooperation but not full integration. Now the biopharmaceutics/formulation evaluation has moved into my group to make sure that the biopharmaceutical/bioequivalence aspects [are considered] while we are looking at the quality. Using IVIVC by looking at the in vivo response and in vitro release, such as the distribution profile to establish the relationship of the model, becomes key in order for the dissolution specification to become more biorelevant.
“We don’t necessarily have answers for all of these topics, but we are considering them,” Moore told the IFPAC participants. “We hold these discussions on a case-by-case basis. So if you or the other people in your firms have some concepts you want to bring forward, I would say definitely come talk to us.”

Topics regarding QbD applications about which agency thinking is beginning to coalesce include good scientific and mathematical practices for developing, verifying and maintaining models, such as for NIR, Moore noted, and more generally what content the agency wants to see in QbD applications as outlined in ICH Q8(R).

At the November APIC conference, ONDQA director Nasr summarized the progress his office has seen companies make on the QbD pathway.

In terms of the control strategy, the agency has seen more focus on in-process control and testing. “Many tests for the drug substance and drug product have been moved upstream rather than relying mostly or only on end-product testing. We have seen on-line analyzers being used for intermediates,” and the implementation of real-time release.

Nasr commented that “many of you were questioning whether the day would come when we would have real-time release testing using process analytical technology.” However, he noted, “we have seen situations where every aspect of the process – from dispensing raw material to blending through making the tablets and coating the tablets – is being controlled and all the testing is being done on-line, and the redundancy with end-product testing has been minimized.”

In offering suggestions for QbD meetings and submissions, Nasr said that his office “would be more than happy for you to come and talk to us first.” He advises firms to make sure that they have the right information to make the discussion productive.

The end of Phase II, he said, is usually a good time to start this dialogue with the agency. “We understand that you will not have all the information, but at least we can start discussing the kind of level of details needed. And the pre-NDA is usually a good time to discuss the format and more details about the application.”

“Key areas” warranting discussion, Nasr advised, include the design space concept for which “there is still a lack of complete understanding,” such as the difference between univariate and multivariate approaches in defining the parameters and which parameters need to be evaluated.

“Design space is not required” in applications, Nasr commented further, “but having a good description of the manufacturing process and defining the parameters used to monitor and control the process is required. So how these parameters were developed and whether they are or not part of the design space needs to be clearly described.”

The ONDQA director added that “if you are using a design space and you are developing such a design space at a small scale and you want to scale up, there may be evidence of some residual risk or areas in the design space where you are not sure about the quality and the control operations. How this can be managed in order to mitigate any potential risk under your own quality system needs to be addressed.” More detail may need to be provided and/or available when the inspection takes place, Nasr said. “The overall control strategy for product quality” needs to be clear, he stressed.

The Gaps That Need Filling

As QbD implementation progresses, the agency is becoming aware of the scientific gaps that still need to be filled in.

One area in particular that has generated considerable attention at conferences is “understanding the link between what that product is and how it works in the patient – that is, integrating the field of biopharmaceutics into QbD,” Moore stressed.

The importance of the issue and the challenges around addressing it were brought to the fore as CDER moved the spotlight onto QbD for large molecules and what OBP needed to achieve in its biotech pilot (IPQ, Sept/Oct. 2007).

GAPS IN THE QUALITY/CLINIC CHAIN

- **Complex molecules**
  - How does degree and type of glycosylation affect protein immunogenicity?
  - How do protein sequence variants affect product efficacy?

- **Complex dosage forms**
  - How can you determine the release rate of a transdermal patch in vitro?
  - How does variability in size and composition of a liposomal product affect drug delivery?

- **Patient variability**
  - How do differences in age, physiology or genetic makeup affect drug efficacy?
Understanding complex products and processes and the quality/safety/efficacy linkages is a place where FDA has more to learn, Moore acknowledged. ONDQA faces similar complexities to those in the biotech arena in terms of complex dosage forms such as transdermal patches, the deputy director noted. The use of models and statistical approaches such as Bayesian analysis in understanding design space is another step on the learning curve, she pointed out.

Challenging regulatory issues are also presented in implementing the modern control strategies inherent in the QbD paradigm.

Among these, Moore commented, are “what kind of instrumentation and controls do you need? How do you look at model maintenance and improvement? And how do you do continual process improvement to do the implementation of these quality-by-design concepts?”

Specific issues, she noted, include: “translating process understanding into effective controls through on-line and at-line methods; effective sampling strategies; feed-back and feed-forward controls; applying modern manufacturing approaches – looking to get to where many other industries are using lean manufacturing, real-time release test approaches, and continuous manufacturing.”

The issue of continual improvement, a basic objective in the QbD approach, is also a challenging one, she noted. “How do you continually update your product and your process such that you are assuring product quality over time, especially when you are talking about process analytical systems, models that you are using, and just the whole matter of knowledge retention, etc.?”

**Continuous Manufacturing Touted By FDA**

One area, in particular, that FDA is focusing on as a significant opportunity for advancing the QbD objectives is continuous manufacturing.

Moore highlighted CDER’s interest in continuous manufacturing at the IFPAC meeting, noting the recent progress that has been made in converting the concept into practice.

She pointed to a diagram of a continuous tablet manufacturing process that includes fully automated testing and real-time release, which she had shown three years ago, as an example of this progress. Whereas the diagrammed continuous process seemed “rather conceptual” at that time, “I don’t think it is conceptual anymore, because I have seen over those last three years several presentations by both industry and academia that are putting practically every aspect” of what the diagram depicts into practice.

At the APIC conference, ONDQA director Nasr also emphasized CDER’s growing interest in continuous manufacturing.
Manufacturing without interruptions with a constant flow of material in and out “fits very well within the concept of quality by design,” Nasr pointed out. “It provides an opportunity to adjust the process to meet the critical quality attributes and allows for continual monitoring and adoption of process analytical technology. It has lots of advantages. It also has some challenges.”

Among the advantages are ease of scale up, Nasr explained. Also “you can use smaller capacity manufacturing equipment and increase the efficiency, reduce the environmental impact, which becomes a very important factor in the industrialized world, and also improve the quality.”

While FDA is “very interested in the concept of continuous manufacturing,” Nasr expressed the agency’s concern that companies not “use some of these approaches without definitely being prepared to address the scientific and regulatory issues that come with it.”

To help address those concerns, ONDQA started a joint research program with the Center for Process Analytical Chemistry (CPAC) at the University of Washington Seattle in late 2008 involving the use of microreactors. The project incorporates CPAC’s “New Sampling/Sensor Initiative” (NeSSI).

“The goal of this project is to enhance our understanding of continuous manufacturing and microreactors and the benefits that can come from their use,” Nasr explained. The potential benefits include improved reactor design, more effective sampling and online analytics, and increased process understanding and manufacturing efficiency over the long term.

He noted that shortly after the project was started, DSM published an article in Chemical & Engineering News (March 2009) highlighting the company’s installation of microreactors in Austria to manufacture an arthritis drug.

The DSM project involves using microreactors to combine three key synthesis steps in generating a few hundred tons of product annually. The advantages projected by DSM from the microreactors include the ability to quickly attain a safe mode of operation that is fast and clean, better control of the process, high yield and ease of scale up.

Biotech QbD Pilot Focuses On Clinical Relevance

In mid-2008, FDA’s Office of Biotechnology Products (OBP) announced that it was seeking pharmaceutical company volunteers to participate in a follow-up QbD pilot for the quality component of biotech product applications submitted for OBP review.

The objective, OBP explained, was to expand on the learnings from the ONDQA pilot and “gain more information on and facilitate agency review of quality-by-design, risk-based approaches for manufacturing biotechnology products.”

[EDITOR’s NOTE: The September/October 2007 and Sept/Oct. 2008 issues of IPQ provide an in-depth analysis of the developments and discussions around the application of QbD to biotech manufacturing and the learnings from the growing industry and regulator experience in the U.S. and Europe with QbD in the small molecule arena.]

In announcing the pilot, OBP expressed a preference for applicants to enter the pilot during a product’s development phase under an investigational new drug (IND) application, as that would facilitate working with the agency on developing and refining the QbD approaches for the marketing application.

The quality assessment under the pilot program encompasses CMC meetings as needed before the submission and during the review process. OBP has encouraged potential participants to discuss their plans with the office before applying. The assessment process is being overseen by the director’s office and an expert cross-disciplinary team, and assisted by CDER’s Office of Compliance in conjunction with the field organization.

With the large molecule pilot, attention shifted to the heightened challenge and complexity of assessing the criticality of quality attributes and linking them to clinical performance as well as the manufacturing process in building a firm foundation for QbD in the biotech arena.

Making these quality attribute/clinical performance linkages was recognized to be a pivotal issue at the biotech QbD workshops which helped define the biotech pilot goals (IPQ, Sept/Oct. 2007). The pathway for tightening these linkages continues to be a key focal point in the biotech QbD discussions.

In describing the goals, application types sought, and acceptance criteria for the pilot, OBP has stressed that the types of data linking attributes to safety and efficacy is an important element.
Commenting on the pilot at the time of its launch, OBP Division of Therapeutic Proteins Deputy Director Barry Cherney pointed out that there are various possible approaches, from platform technology transfer to experimental animal models, that can “really pull out what the critical attributes are in relation to clinical performance. We want to try to receive as much variety in the approaches as possible” (*IPQ*, Sept./Oct. 2008).

One key difference in the biotech initiative was OBP’s specification that the pilot applications provide an “expanded change protocol” (ECP) to house the QbD information involved. OBP is taking the expanded protocol approach to help navigate around the constraints of the CTD structure and the biological license application (BLA) regulations.

OBP explained in announcing the pilot that these expanded change protocols would build upon the successful use of comparability protocols to facilitate manufacturing change for biopharmaceuticals. The ECPs should describe the applicant’s QbD, risk-based approach, “linking attributes and processes to product performance, safety and efficacy,” in support of the broader spectrum of changes involved.

Along with the incorporation of the ECP approach, the new biotech QbD pilot involves another significant gear shift from the small molecule pilot in focusing on the drug substance rather than the formulated drug product. The formulated drug product was the focus in the applications submitted under the ONDQA pilot, Cherney commented, since in the small molecule world “that is where a lot of the variability exists.” By contrast, for biotech products “the API is the major source of variability.”

Like the small molecule initiative, the biotech pilot program is targeting both original applications and postapproval supplements.

The pilot goal is ten post-approval supplements, which could cover QbD approaches to unit operations, he explained. OBP has entered four supplements into the pilot – two monoclonal antibodies, one therapeutic protein, and one that covers multiple products, which Kozlowski views as “an important area.”

As of the beginning of February, the biotech office had held seven meetings with pilot sponsors and has been tracking the questions that have arisen during these meetings.

Most of the questions related to monoclonal antibodies (25) with four involving other therapeutic proteins. Design space has generated the most questions (13), followed by risk assessment methods (6), control strategy (4), expanded change protocols (4) and the adequacy of small-scale models (3).

Kozlowski quipped that the meetings all went basically the same way: “The company presents us with their approach and asks if the agency agrees. The agency says, ‘yes, we agree in principle, but until we see the actual data we can’t answer.’ So it isn’t very hard to predict the interactions.”

Commenting on some of the issues that have been raised (see box on p. 25), the OBP director cited the concern of “what knowledge can be moved across different products.” In the supplement context, for example, the question has been framed in terms of site transfers, an issue that OBP is working closely with the CDER compliance office to handle, Kozlowski said. In general in dealing with the complexities of biotech products, he added, “it is extremely important to figure out how to work with the GMP side in terms of doing this [QbD] well.”

**CDER MAPPs Out Biotech Reviewer/Inspector Roles**

The lifecycle nature of the QbD/Q8-10 quality regulatory paradigm and the interdependence of its development, risk management and quality system components is forcing the US and EU regulatory agencies to rethink the way their review and inspection components have been structured and have interacted.

A compelling expression of that need to clarify anew these interrelationships is a recent directive in the agency’s “Manual of Policies and Procedures” (*MAPP*4730.3) defining the roles and responsibilities of OBP and the Division of Manufacturing and Product Quality (DMPQ) in CDER’s compliance office.
The MAPP is part of a “process improvement initiative to better coordinate the evaluation of applications” in view of the new lifecycle framework.

Among those participating in developing the MAPP were OBP’s Cherney, Kozlowski and Chana Fuchs, and DMPQ’s director Richard Friedman and deputy director Nicholas Buhay. Joseph Famulare, who was then deputy director of CDER’s compliance office (he joined Genentech this past fall) played an oversight role.

The document contains separate sections defining the purpose, background, references, definitions, policy, responsibilities, and procedures.

The purpose of the MAPP is to: “ • ensure product quality as it relates to safety and efficacy of the product • provide a team approach to product quality evaluation of biologics licensing applications • define clear roles and responsibilities • establish work processes that are effective, and • develop a system that ensures problems are resolved in a timely and professional manner.”

The background section notes a need for the agencies to internalize QbD concepts and form “synergistic (multi-disciplined) collaborations.” It also states the need to develop a “shift from review-based approvals for ‘low risk’ postmarketing changes to annual report evaluations and compliance- and inspection-based confirmations and/or evaluations.” As a matter of policy, the document details setting forth how reviewers and compliance officers will “work together to evaluate both original BLAs and supplements.”

Responsibilities for how DMPQ and OBP will meet and communicate with each other are delineated. Of note on the OBP side, the document states that the new approach will involve reviewers participating in inspections “over the biological product lifecycle.” They will take part in these inspections, the directive explains, by focusing on issues related to structure and function, and will assist in writing

---

**CDER DEFINES BIOTECH REVIEW/COMPLIANCE ROLES IN SHEPHERDING QBD**

A recently released internal directive for CDER’s “manual of policies and procedures” (MAPP 4730.3) provides a breakdown of the responsibilities for evaluating biotech applications between the Office of Compliance’s Division of Manufacturing and Product Quality (DMPQ) and the Office of Biotechnology Products (OBP). The MAPP reflects the need for the application review and GMP compliance groups to work more closely together in advancing the ICH Q8-10/QbD objectives.

The responsibilities of the Office of Compliance DMPQ include the following:
- Review facility, equipment, and procedures in coordination with BLA and supplement submissions.
- Lead in the assessment of the manufacturing and control of drug product as it relates to contamination/cross contamination control, sterility assurance, and microbiological product quality, and conversion and use of facilities for multiproduct production. Drug substance assessment is largely led by OBP, but with DMPQ involvement. Both include desk review plus inspection.
- Provide IND assistance, as requested by OBP.
- Plan collaborative inspections based on firm’s compliance history and chemistry, manufacturing, and control (CMC) facility information.
- Share evaluation of CMC process validation and robustness with OBP.
- Provide the lead on inspection policy, and enforcement of current good manufacturing practice (cGMP) policy.
- Take the lead on evaluation and enforcement of the Pharmaceutical Quality System

The responsibilities of the Office of Biotechnology Products (OBP) will include the following:
- Review product structure, relationship between structure and function, and impurities (including contaminants).
- Review process controls throughout the biological product life cycle for impact on structure/function and impurities.
- Participate in inspections over the biological product life cycle (preapproval inspection (PAI) and surveillance) with a focus on issues related to structure and function. This may include the following:
  - Assistance in evaluation of deviations, investigations, and process robustness/control
  - Batch record/life cycle relationship to attributes
  - Analytical assays
  - Take part in inspections for reviewer education
  - Participate in Biological Product Deviation Report (BPDR) evaluations (led by OC, with assistance from OBP on assessment of product impact).
inspection observations and providing comments on the company’s responses.

Attachment A provides roles and responsibilities for assessment of the process validation and facility/equipment qualification component of BLAs, and what role members from DMPQ and OBP will play in that process. For example, the DMPQ assessment leader will review supplier/site qualifications, and the OBP will lead the review of the process for intermediates and drug substance synthesis.

Attachment B clarifies the responsibilities of OBP and DMPQ for assessing the manufacturing and product quality information in the various drug substance (S.2) and drug product (P.2) sections of the Common Technical Document (CTD). For example, regarding drug product manufacturer inspections, DMPQ is tasked with identifying the sites for PAI inspection, planning the inspection, and identifying and leading the team, while OBP provides support for the inspection planning and participates in the inspection.

Industry groups in the U.S. and Europe have been working to support the regulator QbD efforts with mock case studies.

A small molecule case study on a mock tablet analgesic product “ACE” by an industry working group under Conformia’s direction was followed by a similar effort in the large molecule area on a monoclonal “A-Mab,” which was published this fall. Following the development of its small molecule mock “Examplain,” the European Federation of Pharmaceutical Industry Associations (EFPIA) began work on a mock case study “Mockestuzumab” that is nearing completion. [EDITOR’s NOTE: The mock efforts are discussed in detail in the Sept./Oct. 2008 issue of IPQ.]

The “CMC Biotech Working Group” on A-Mab included experts from Abbott, Amgen, Lilly, Genentech, GlaxoSmithKline, MedImmune and Pfizer, under the leadership of Kenneth Seamon (former FDA official and now Cambridge University professor) and John Berridge (former Pfizer official and ICH Q8 expert working group member). The A-Mab study is impressive in its depth and breath and is publicly available.

At the QbD/PAT IFPAC workshop, Kozlowski highlighted the contribution of the A-Mab effort (see Appendix II). 

“There is a lot of meat in the case study and a lot of real data, some of which was taken from the companies’ own experience, to think about,” he commented. A-Mab is not a template for a QbD submissions, a definite source of regulatory definitions, nor the only scientific approach to biotech QbD. However, Kozlowski stressed, it is a source of “challenging and very well thought out examples” and makes a “very useful” contribution to “QbD implementation for complex molecules.”

The Center for Biologics Evaluation and Research (CBER) has also been updating its guidance to keep up with the advancing science – with vaccines and cell/tissue products getting particular attention.

In early March, CBERT announced the release of a final version of its guidance to industry on “Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications.” FDA had released a draft of the guidance in 2006, and industry comments on the draft were incorporated into the revision. The guidance replaces the information specific to vaccines provided in CBERT’s 1993 “Points to Consider” in characterizing biologic cell lines.

In line with the overall Q8-10/QbD thrust toward real time release, FDA also issued in late February a final version of the 2008 draft guidance addressing information to include in human and animal drug and biologic applications in support of parametric release for products terminally sterilized by moist heat processes. Most of the changes in the final version involve clarifications to the draft.

FDA Generic Drug Review – Through QbR to QbD

In 2007 the Office of Generic Drugs (OGD) unveiled its Question-based Review (QbR) initiative, designed to implement the concepts of the cGMPs for the 21st Century initiative in the generics drugs world. QbR consists of a series of questions with emphasis on quality-by-design and pharmaceutical development knowledge for applicants to answer as part of the application process.

QbR is intended to focus the review on understanding the key attributes of drug product quality and the specifications and manufacturing controls necessary to assure it. The approach encourages sponsors to share their pharmaceutical development knowledge and promotes their understanding of how formulation and manufacturing process factors affect pharmaceutical quality. This understanding, in turn, is designed to lead to more relevant specifications and manufacturing controls.
At IFPAC, OGD Chemistry Associate Director Frank Holcombe explained how working under QbR has changed his office’s review process.

Holcombe noted that historically generic drug approval resulted from data demonstrating that a company has a process that it can use to make a batch of product that fits all the requirements. Under the QbR paradigm, reviewers are taught “not to look at the data but the justification that the data is supposed to represent.”

“What we are moving into is an understanding of the products and processes, and the intentions of the product,” Holcombe stated, “so that the properties of the single batch in the application becomes less and less important. We are trying to make this more an exercise in evaluation and justification of tools and activities than submitting data and just straight information.”

“It is not the job of the reviewer in our mind anymore to figure out what is in the application,” he explained. “It is the job of the reviewer now to decide whether the product has been suitably justified by the firm.”

QbR also requires a change in approach by the companies submitting applications. Holcombe summed it up, using an example: What a firm needs to think about is not “submit stability data,” but “what specific container-closure attributes are necessary to ensure product performance,” he said.

OGD has provided examples of completed QbRs to generic drug manufacturers to help them understand the kinds of information expected in those applications. In addition they have posted a Q&A document on their web site, given presentations, and hosted workshops. OGD is also working on a series of publications that will focus on the common deficiencies the office has noted in applications over the past 20 years, and how they would be viewed under a QbD paradigm.

Teaching both industry and review staff how to apply QbD principles is important, Holcombe stressed. Noting that “we are asking for some of this information now,” he maintained that “eventually it will be required, because it will be a key component under Q8-10 for how you build your quality system and allow industry responsibility for change or variations in the future.”

More than 90% of ANDA submissions are now in the QbR format. OGD has evaluated the QbR process and believes it is working well, but is striving to improve it further. A working group has also been created to develop additional QbD examples for generics.

At the ISPE annual meeting, CDER’s Morefield noted that modified release products have been getting particular attention at recent industry/agency generics conferences and OGD is reviewing its policy in this area.

“They are looking to try to improve the generic modified release products that have been coming forward,” she stated. OGD is considering how QbD might be used for modified release products to “mitigate some of the quality issues that they have seen,” and OGD and industry have formed parallel working groups on the issue. As a result, she said, there may be changes to the ANDA submission requirements for modified release products in the future.

While the transition to the question-based review format is improving the quality of ANDAs received and the overall review process, it has not solved the problem of the growing backlog in the number of applications awaiting review.

The number of ANDAs approved by the generics office steadily increased from 241 original and 69 tentative approvals in 2001 (310 total) to 494 and 188 tentative approvals in 2007 (682 total). However, the number fell off to around 600 combined approvals in 2008 and 2009. Meanwhile the number of ANDAs received has grown at a faster pace, basically tripling from 307 in 2001 to 880 in 2007 when the number leveled off.

With little increase in OGD resources, the surge in ANDAs received over the decade has contributed to a significant increase in the backlog of unreviewed applications and the average time to approval, which has now reached over two years.

Those ANDAs coming in also present additional challenges. An increasing percentage are from less-regulated regions such as India and China, where inspection oversight is more resource intensive, and involve companies with which FDA may not have as much or any familiarity. Supply chains have gotten more complex, further increasing the agency’s regulatory challenges both for new applications and for changes to those already approved. The dosage and delivery modalities are also growing more complex and OGD is looking for better understanding both by the applicant and the reviewer, as the QbR approach demonstrates.
OGD is now in the process of adding 50 additional scientists to help address the backlog and keep up with the current flow. Most of the new hires will be involved with chemistry review.

At the University of Georgia’s annual GMP conference in mid-March, OGD Deputy Director Robert West cautioned that the hiring would not provide a quick fix for the backlog problem, since experienced reviewers will have to be pulled away from the review process to do all of the training required.

OGD has different approval cycles going on during an ANDA review, including chemistry, microbiology and labeling, West said, with the problem that “you get one or two of those under control and the other pops out of control.” The micro cue had been problematic with two-year or more delays, but putting more people there brought that component under control, he said.

Without the user fee support to push down review times, West pointed out that “it takes longer today to approve a generic drug than it does to approve a new drug.”

At the annual meeting of the Generic Pharmaceutical Association (GPhA) in mid-February in Boca Raton, Florida, FDA Commissioner Margaret Hamburg discussed the regulatory challenges for generic drugs and the need for more review resources, potentially supported by industry user fees, to keep up with the expanding workload and address the current backlog (see box on next page).

Noting that generics usage has climbed to 75% of the Rx marketplace, Hamburg emphasized the importance of the generic drug industry in the public health equation, the role of the QbD effort in problem prevention, and the regulatory challenges created by the globalization of the application pool and the supply chain.

ICH Vision Taking Shape In EU With PAT Team Help

The EU is also beginning to gain experience with submissions that have QbD elements. After a slow start, the numbers of QbD applications being submitted in Europe are increasing, with companies that receive approval filing subsequent applications for other products.

Speaking at the ISPE annual meeting in November, EMA Scientific Administrator Evdokia Korakianiti provided an update on her agency’s experience with QbD submissions (see Appendix III).

At that time, 16 new product applications with QbD approaches had been received. Four of those applications contained a design space accompanied by a thorough control strategy, while the remaining 12 had some elements of QbD incorporated in them. Four variation submissions had been received involving QbD, and two scientific advice requests had been made.

Most of these submissions came from big pharma, and they were mainly for chemical active substances, although there
FDA COMMISSIONER HAMBURG ON GENERIC DRUG REVIEW CHALLENGES

At the GPhA annual meeting in mid-February, FDA Commissioner Margaret Hamburg discussed regulatory challenges for generic drugs and biosimilars and the need for more review resources to keep up with the expanding workload and address the current backlog. [For Hamburg’s full presentation at GPhA click here.]

Regulatory science is the science needed to evaluate, ensure and monitor a product’s safety, effectiveness, potency, quality and performance. We need to advance this science to include new tools, methods, assays, standards, and models that will help speed the development, review, and approval of medical products. Regulatory science may not be as sexy as discovery science…but it is really important and it really matters if we want to get products to people.

Let’s start with biosimilars. As you know, there are a lot of concerns. How will we regulate these? Which framework will we use? These are important questions because patients want and need more access to these products — and, of course, I know how much promise they hold for your industry. Understandably, you are eager for answers.

First, we must develop a robust biosimilar approval pathway, which is more than what any short-term political patch can provide. After all, biosimilars raise questions for regulators that are far more complex than those posed by traditional generics. For particular products, will we need clinical studies beyond bioequivalence? Is interchangeability possible? How will the approval process differ from the Biologic License Application process?

We will address these questions as we work together over the coming months, which I look forward to, but I can say now that there will not be a ‘one-size-fits-all’ approach. There will, rather, be a science-driven, case-by-case decision-making process rooted in the regulatory studies that I would encourage your industry to support—as the FDA will—at this crucial time. The FDA can advance some of the science, but we can’t do it all.

That may account for emerging generics, but what about the many existing generics? Even as we try our best to clarify to consumers that generics are safe, effective, and equivalent — and shortly after I became Commissioner, we revamped our website to dispel the myths about generics that persist — your industry can also work to better assess outcomes and act upon your findings.

Just as the FDA is beginning again to act aggressively and agilely in response to any credible report of impending problems, I ask that you, too, take public concerns seriously and rigorously investigate any potential therapeutic inequivalence. This too is a component of regulatory science. I was encouraged to learn that some of you are, in fact, starting to support such studies examining these concerns. I believe you are making the right decision— for your bottom line, for your reputation, and above all, for your consumers.

Finally, let me mention that as we all know, no one benefits from a pending-application queue that will soon hit the 2,000 mark. This is simply unacceptable. Uncertainty and delays are costly to consumers, costly to you — and hurtful to the public. But the unprecedented spike in generics applications has simply outstripped our capacity to properly review, which must remain our foremost focus.

The solution lies in resources. We have already begun to use the $10 million that Congress allotted to our agency to hire 50 additional scientists to address the generics-application backlog. But without action from your industry, too — without your support for a fair system of user fees — we simply cannot achieve for the public what we otherwise could. I know we have an essential part to play, too, in providing your industry with meaningful benchmarks...and in performing to those goals.

We very much want to work with you to see generic drug user fees enacted this year. Adequate and reasonable fees will be key to both more rapid review and to better surveillance. The merits of the former, I know are obvious to everyone in this room. But as I was just discussing, a robust inspectional presence is also critical to consumer confidence in safe and high-quality products. And with the industry becoming ever more global, the continuing threat of intentional economic adulteration, and the increasing complexity of supply chains, we face tremendous challenges in our efforts to prevent or detect problems early — and user fees can assist us in meeting those challenges. So I do hope we can return to the negotiating table soon.
appears to be an interest by smaller companies and for biological products as well, Korakianiti said.

The EMA official is not surprised by the low numbers of applications. “It is normal that industry would come and test the waters” and start slowly until they are comfortable with the process, she commented. “It is a learning process both for industry and for us.”

Irish Medicines Board (IMB) Senior Scientific Advisor Michael Morris expanded on that theme at the ISPE meeting. He noted that companies tended initially to introduce new technologies to existing products using variation filings because the perceived risk is lower.

“The advantage here is if you introduce a change and the regulatory authority doesn’t approve it, at least the product is still on the market,” Morris explained. More recently, however, he noted, companies have begun to make applications for a marketing authorization using the centralized procedure, or at the earlier stages are using the scientific advisory requests to bring in QbD concepts.

“That is very encouraging,” Morris stated, “because I think it reflects the fact that there is a growing confidence that the system is working. We have also set up an informal work sharing process, and EMA has established a specialist PAT team.”

The EMA has defined a three-stage approach to implementing the ICH Q8-10/QbD vision: • identify the knowledge gaps • build the knowledge needed to close the gaps, and then • share that knowledge among all involved.

The PAT team is the central player in this approach – promoting dialogue, providing training to assessors and inspectors and advice to industry, and driving harmonization in the assessment and inspection of QbD applications.

The team acts as a gateway for both small molecule and biologic QbD applications in the EU and assists industry by reviewing the applications prior to submission. It includes representatives and the chairs from the EMA’s quality, biotechnology and inspectorate working parties, five quality assessors, four GMP inspectors, plus an observer from EDQM.

The team interacts with many organizations, including the PAT topics groups from EFPIA and ASTM, and the FDA. It also consults with equipment manufacturers to provide better understanding of in-process and PAT applications.

The team has been working with the European Directorate for the Quality of Medicines (EDQM) on the impact of PAT on the European Pharmacopeia (EP) and its sampling and testing standards, and helped spur the formation of an EDQM PAT team in 2009.

Membership of the EDQM team includes experts from industry, academia, and regulatory authorities. Several of its members also participate on the EMA PAT team. Initially, the EDQM team has focused on providing input to the EMA NIR guidance and examination of uniformity testing for larger sample sizes of unit dose solid preparations and the development of appropriate acceptance criteria.

Speaking at the PDA/EMA conference last October, Lina Ertle, who represents the French agency AFSSAPS on the PAT team, emphasized the importance of industry working with the team.

“Each company who wishes to submit a dossier containing QbD or design space can contact us first before submitting the dossier to EMA,” she advised. “This is very important because we can give advice and we can give the first view of the regulator on the approach.”

At the ISPE annual meeting, IMB’s Morris agreed. “It is very important to engage in dialogue with the regulators, I would say as early as possible,” he emphasized.

The PAT team has developed Q&As to clarify regulator expectations and address industry concerns, and has been working with EFPIA on its mock submissions for QbD/PAT applications.

Additionally the team has developed guidance for assessors, inspectors and applicants on the impact of PAT/QbD on batch release, the assessment of quality, and inspection practices. These documents are still in draft and not yet available publicly.

Although the PAT team currently plays a central role in QbD submissions, the long-term EMA vision is to institutionalize these concepts and practices, potentially disbanding the team when its mission is complete.

Workshops, New Guidelines Support EMA Efforts

EMA and EFPIA held a joint workshop in 2008 in Ireland, and a two-day session in London in September 2009, to discuss QbD implementation and case studies.
At the 2008 workshop, the discussion centered around quality by design and identification and control of the critical processes and steps. Participants debated the definition of ‘critical steps,’ but agreed that critical steps need to be adequately controlled. There was also discussion on the role of the Qualified Person (QP) in this process.

The first day of the 2009 meeting was a closed session. Six companies presented QbD case studies to the 120 regulators present, going into detail on their products and processes for discussion and feedback. Four of the cases involved small molecule products and two involved biotech products.

The second day of the meeting focused on lessons learned from the same case studies, which were presented in a more general fashion to protect confidential information. A representative of the company involved in the case study and a regulator provided their perspectives on each of the case studies.

The six case studies involved: • an integrated application of a QbD development approach across chemical and formulation manufacturing processes (Merck Sharpe & Dohme) • continuous quality verification (Pfizer) • use of in-line NIR spectroscopy to monitor segregation of a powder blend in a tablet press (Lilly) • the use of in vitro and in vivo data to define both design space and control strategy (AstraZeneca) • QbD development of a novel therapeutic protein (Wyeth), and • utilization of QbD principles for the management of post-approval changes for a novel recombinant monoclonal antibody (Amgen). Additional information on the case studies is available on the EFPIA website.

EMA is moving forward with several guidance efforts, which will complement the work of the PAT team. These include: • a new guidance on NIR • a broadening of its existing parametric release guideline beyond terminally sterilized products to cover real time release testing and related PAT concepts and technologies • and a revision of its process validation guideline.

Industry expressed a number of concerns with the first version of the NIR document, which are being taken into account in the revision.

During the last week in February, EMA released both a draft of the “Guideline on Real Time Release Testing” (formerly Guideline on Parametric Release),” and a “Concept Paper On the Revision of the Guideline on Process Validation.”
The guideline highlights the requirements that have to be fulfilled in the application as well as those related to preapproval and GMP inspections.

Also on the horizon are EMA efforts to develop a parallel mock CTD S2 (drug substance) submission in line with Q11, and possible guidances on the impact of QbD and PAT on specifications and GMP inspections.

**Ireland Following Suit With Industry Collaboration**

The experience of EU national authorities implementing Q8-10 is following the EMA pattern. IMB’s Morris provided insight into how the implementation process is unfolding in Ireland, where his agency is actively helping drive forward the overall initiative.

Morris noted that, while Ireland is a relatively small country, it is one of the largest EU bases for manufacturing pharmaceutical products – housing multi-national and domestic companies that produce both drug substances and drug products. The Irish Medicines Board (IMB) is the regulatory authority for Ireland for both human and veterinary products and medical devices.

According to Morris, IMB’s experience with QbD indicates that many companies are placing more emphasis on better characterization of their products and processes and following an enhanced approach to control, although relatively few QbD applications have been submitted.

**At the ISPE annual meeting, Morris explained that his agency is interested in having a dialogue with industry regarding QbD applications.**

“IMB wants to listen, support applications, and we are very positive to the idea of additional knowledge about manufacturing processes being developed,” he noted. “We want to respond to these ideas, give advice where we can, but not necessarily be seen to be leading. I personally, strongly believe the expertise is in the hand of the manufacturers rather than with the regulators.”

Morris noted that while the IMB is very receptive to dialogue with the industry, for this dialogue to be effective the regulators need to be provided with the appropriate data, and where possible, to have access to the scientists themselves. “We need to have enough information to understand the processes without having data overload – it’s a fine balance,” he said.

Morris discussed his agency’s experience with QbD applications and discussions, citing two examples involving: an approved product where a design space was being proposed; and a new product still in development, where the firm was seeking input on proposed design spaces.

In the first example, a manufacturing firm in Ireland submitted a variation through the worksharing procedure for an oral product marketed across the EU. Another member state was the rapporteur with Ireland serving as co-rapporteur. The proposals from the company received a very positive response, but a number of questions emerged.

Following the discussions, IMB carried out a one-day focused inspection on the specific process, with one inspector and two assessors. Morris was one of the assessors. “Many of the questions that were asked were immediately answered,” he noted.

“We were able to dialogue with the company at the site,” he explained. “We agreed with their approach, and the successful outcome was subsequently agreed to rapidly by all the member states. The company had the advantage of standardizing the manufacturing dossier as regards the manufacturing process in all the member states.”

In the second example, a company chose to submit questions using the scientific advice procedure regarding a new product containing a new drug substance – proposing design spaces for both the drug synthesis and drug product control. “It was in early stages,” Morris explained. The company had performed preliminary DOE and developed some data, “but the questions posed by the applicant were not all able to be answered very clearly due to the limited data presented – it was too early in the process.”

Morris stressed that to make such consultations meaningful, “we need to have information on the analytical procedures and processing equipment, including working principles and manufacturing capacities, but we don’t need massive detail. We need to know the science behind the technique,” he stated. “This helps us to understand a particular element, but without the operating manual.”

**To further the QbD dialogue in Ireland, the IMB created its own PAT team that parallels the EMA team.**

The IMB PAT team is a multidisciplinary team with input from assessors and GMP inspectors who have human and veterinary, chemical and biological expertise. This team acts as a focal point for reviewing QbD applications, provides a forum for stakeholder dialogue, and acts as liaison with...
EMA, EDQM, and Pharmachemical Ireland, the trade association for manufacturing companies based in Ireland.

**FDA, EMA Work On Clearing CMC Change Pathway**

The application of QbD across the product lifecycle pushes to the surface the issues around regulating the manufacturing changes that need to flow in this continuous improvement framework.

Regulators in the ICH regions are making a concerted effort to unleash the power of science and technology to improve products and processes by reducing the regulatory burdens and constraints involved in the change process. The question is how they make sure that the firm’s quality system is up to the change management task.

Industry and regulators have been debating how to reduce the constraints created by their marketing applications on the one side and the GMP process validation and change control requirements on the other.

FDA has released a draft of a new process validation guidance in support of the lifecycle quality paradigm (*IPQ*, July/August 2009) and EMA has begun redrafting its process validation guidance to follow suit as the just released concept paper explains. The new EMA real time release draft guidance is another example of the effort to clear the pathway for more effective control mechanisms to be put in place.

Both regulatory bodies have also been taking steps to reduce manufacturing change filing requirements where they inhibit process and product improvements and create unnecessary burdens on both companies and reviewers.

The encumbrances of the multistate European system have resulted in its lagging behind the US in instituting more progressive policies. However, the EU has been actively working to update its rules and guidance to better accommodate the QbD/continual improvement objectives.

In late 2008, the European Commission published a revised “variation regulation.” A pair of guidances followed in January 2010 spelling out the revised variation filing expectations and procedures. The two are entitled “Post-authorization Procedural Advice: Human Medicinal Products,” and “Q/A List for the Submission of Variations.”

At the end of February, the EMA also released a “concept paper” on the need for revising its “Guideline on Stability Testing for Applications for Variations to a Marketing Authorization” to bring it into line with the new changes in the variations regulation and supporting guidelines.

The new EMA regulation/guidance brings the EU closer to the US model. Under the new EU policy, the categories of “minor” variations considered to have little or no impact on product quality and not requiring preclearance are clarified and expanded, and the provision is made for post-approval change management protocols.

Highlighting the significance of the new regulation and guidances at the IFPAC February workshop, EMA’s Korakianiti stressed the improved flexibility the revisions provide. “Post-approval regulatory flexibility was not possible until the end of 2009,” she stated. “We are quite happy to say that now this has been taken care of.”

Korakianiti commented on the new EU provision for post-approval change management protocols: “The US has quite some experience with them – they are the so-called ‘comparability protocols.’ Such a protocol will describe the specific changes that the company would like to implement during the lifecycle of the product and how these would be prepared and verified,” the EMA regulator noted.

This is a new concept for Europe, Korakianiti stated, “and there has been a lot of brainstorming with regards to what types of changes could be allowed in these protocols.” For example, there are questions regarding whether the use of one protocol affecting all CPPs in the same process would be permitted and whether additional studies or pilot data would be required to support the variation.

At the ISPE annual meeting, IMB’s Morris discussed manufacturing variations in the context of the “Worksharing Program” which the EU began in 2006. The program is intended to encourage companies to make QbD-type changes to existing products.

“The idea of dealing with a large number of competent authorities was seen as problematic, and seen as an obstacle to bringing in PAT, quality by design, and that type of application,” Morris explained. “That is an important point, and that is one of the things this procedure is designed to get around.”
Under the worksharing program the EU national authorities agree to appoint two rapporteurs from different member states to carry out independent evaluations of the change. The evaluations are shared with the member states, and those states agree to accept the report. All member states where the product is marketed can participate and receive the assessment report.

“The outcome is not binding – it can’t be,” Morris explained. “It is an informal procedure. However, in practice it has worked.”

Regulators in the US have also been working to provide additional flexibility in handling post-approval changes.

A new draft guidance on supplement reduction for CDER-regulated products is expected to be released soon for public comment. It will cover both small molecules and biotech products.

At the ISPE annual meeting, CDER’s Morefield commented on the pending draft. Applying the principle that changes which are essentially administrative and low risk do not require extensive CMC review, the draft guidance will lower the reporting requirements from CBE-30 and CBE-0 to annual report for over 40 categories of changes, she said. These changes include new testing sites, oral solid dose packaging site changes, and tightened specification changes.

CDER’s Nasr shared his vision of the future of reporting changes at the IFPAC pre-conference workshop in response to a question asking whether all changes may someday be managed solely by the manufacturing firm’s quality system.

“We cannot give back responsibility to the manufacturer to manage any type of changes without having appropriate regulatory oversight to make sure that the products in the market have the necessary quality, safety and efficacy,” Nasr replied.

However, “I would think that sometime in the future rather than having three categories of supplements, you may have only two – changes that are low risk that could be reported in annual reports and the high risk changes that will still need to be submitted to the agency for approval,” he stated. Manufacturers who have a good understanding of their products and processes and a robust quality system “may not need to have this CBE 0 category, and some of these changes would be moved to annual report. That is what I think could happen in the future,” Nasr said.

**Risk Management – What’s The Score?**

As regulators and industry embrace the concepts in ICH Q8-10, the importance of risk management as a QbD enabler and the need to understand and implement it appropriately is becoming clearer. Risk assessments submitted in applications to be meaningful to reviewers must be supported by good models and good measurement systems, both of which are subject to error and variability.

**Risk assessment-related issues that continue to percolate are how the criticality of factors is determined and how to handle factors determined to be non-critical.**

Speaking at the PDA/EMA conference last Fall, AFSSAPS’ Ertle addressed these concerns. “We have an issue with the critical vs. non-critical,” she stated, including “the scoring system and the threshold the applicant is submitting,” which should always be justified. This is a “big issue for assessors and for inspectors,” she said, who have to work together to evaluate the risk assessment.

Frequently a critical attribute will have a severe impact coupled with a high detectability, Ertle explained. However, “the detectability is very much linked to the quality system you have in place. This is why the assessor would ask [the inspector] if they are certain the firm can detect this critical failure very quickly in their system.”

This interaction with inspectors is pivotal to an assessor’s ability to make judgments. The assessor needs to know whether “the inspector who is familiar with the site [believes] the quality management system can support such a quality risk analysis”.

Ertle also stressed the need for critical parameters to be controlled, adding that they “remain critical even if they are controlled,” because they have been “identified from the beginning to have a high impact on the quality of the product.”

The question of subjectivity in risk analysis surfaced at the ISPE Annual Meeting in a panel discussion. An audience member asked the panel of regulators if there is a way to tell when poor decisions have been made during a risk assessment exercise.

“It makes us nervous too,” CDER’s Morefield responded. “I don’t know if there is any way you can absolutely prevent a mistake,” she added, but there are ways to minimize a poor risk assessment outcome.
“Try to get the people who actually have the expertise and knowledge together and meet as a team,” she advised, “because with team thinking, you will have a wider variety of experiences and expertise that can be used, you will be less likely to make poor decisions.”

Morefield also recommended generating data afterword to confirm the decisions made during the assessment. “Generate some data to verify that what the risk assessment produced is the reality.”

“Also look at the detectibility,” she advised. “If you put controls in your control strategy that can detect if there was a failure, then you have a backup…that will catch it.”

Another concern to regulators is having the amount of information they need to assess the criticality of factors. At IFPAC, EMA’s Korakianiti stressed the need for this information to be specific in application submissions (see Appendix III).

“In the case of risk assessment,” Korakianiti noted, “quite often there is no information or minimal information explaining the coding of the variables in an FMEA. What we might receive is a scored table with no interpretation of how this scoring has been developed, and of course this would raise a question.” In addition, regulators would like to see a justification for how the variables for further study were selected, she said.

**Design Space Still Contains Some Rough Edges**

Design space is another QbD building block whose value is becoming better understood while questions are emerging on how that value can best be realized and with what regulatory implications.

Expectations for what should be included as part of the design space in a QbD submission are continuing to evolve. “To be honest, even between regulators, we do not agree on what should be in the design space and what should not be in the design space,” Ertle admitted at the PDA/EMA meeting.

CDER biotech official Kozlowski, speaking at the IFPAC conference (see Appendix II), made the same point. “There is a real challenge here to think about what is in a design space,” he noted. “I don’t have an answer – there aren’t answers for a lot of these things…. Are only CQAs which drive CPPs used in the design space?” Does it include process parameters that are not critical?”

**The theme of critical versus non-critical parameters and their inclusion in the design space has been explored by the EMA PAT team. Ertle, a member of that team, offered insight into their perspective.**

Whether non-critical parameters are part of the design space “is not clear for now. But I can give you the PAT team perspective,” she said, noting that there is not good agreement between the national competent authorities.

“When you performed the design of experiment, that non-critical parameter had a fixed range,” Ertle pointed out. When applicants propose that this non-critical parameter is not part of the design space, they conclude that its range can be changed or it can be replaced by another parameter.

“What about the design of experiment that you have performed?” she asked. “You have to demonstrate that the non-critical parameter is really a stand-alone parameter - that it is completely independent and it has no interaction at all with critical parameters” for this claim to be plausible.

Some applicants contend that the non-critical parameters should not be part of the dossier in the context of design space. “But the PAT team doesn’t agree,” Ertle said. “For
Now it is not clear for us how a non-critical parameter can be a stand-alone, a completely independent parameter.”

FDA’s Elaine Morefield, speaking at the ISPE annual meeting, expressed a similar concern. “If you forget the assumptions and you go and change things you held constant in your experimentation,” she pointed out, “it may have changed the results of your experimentation.”

Morefield provided a note of caution: “All you have is somebody’s opinion that those things were not critical. They might in fact be, and you might get surprised. So you will need to take that into consideration when you are using a design space and making changes.”

Another emerging area of concern is design space scale up and transfer. Initial design spaces are defined in development at lab scale, then must be transferred to manufacturing, and perhaps even between manufacturing sites.

Ertle noted that to date the EU regulatory authorities have not seen a protocol for design space transfer. In some cases, applicants have stated that their processes are size and site

---

**DESIGN SPACE AND RISK MANAGEMENT ISSUES FROM CDER BIOTECH PILOT**

The following are design space and risk management issues the agency has raised in meetings with applicants to FDA’s biotech QbD pilot program. CDER OBP Director Steven Kozlowski’s comments on these concerns at the WCBP and IFPAC meetings are included.

**Design Space**
- **Factor choices:** Are you looking at raw materials in the factors you are studying?
- **Prior knowledge base:** How are you supporting it? What is in it?
- **Appropriateness of the experimental design and statistical analysis**
- **Impact of assay variability on design space:** What are the statistics you are using to define the design space?
- **Viral clearance:** Relationship, if it wasn’t specified.
- **Linkage to other steps**
- **Claims for scale in design space:** Sometimes it wasn’t so clear whether scale was meant to be included or not.
- **Protocols as part of a design space:** This is almost built into the current way the system works. But could you claim a bigger design space if you share exactly how you would evaluate movement within that design space?
- **CPPs alone do not define a design space – assurance of quality does:** Is it only CPPs?
- **Limits for parameters that may not be critical parameters – relationship to design space**

**Risk Assessment**
- **Process capability in CQA determination:** Were they using process capability in determining critical quality attributes? According to the ICH definition, it isn’t appropriate.
- **Independence of factors:** Are factors independent when they made these assessments?
- **Clarity of terms:** What do you mean when you say critical, key, or non-key?
- **Consistency in scoring:**
  - **Uncertainty scoring:** Sometimes scoring for uncertainty was unclear – how it impacted things. You can imagine that something which has a low risk of causing a problem but a high amount of uncertainty should be a bigger problem than something with a low risk and no uncertainty, whereas uncertainty doesn’t impact high risk things the same way.
  - **Qualitative versus quantitative scores:** Very qualitative descriptions were hard for us to understand.
  - **Justification for severity cutoffs:** 40% change in PK – why is that a cutoff for a certain level of severity as opposed to 25% or 20%?
  - **Criticality continuum:** Many companies, or at least one company in particular who met with us, said they really can’t have a threshold for CQAs, it is a continuum, and the control strategy should match the criticality as opposed to being an absolute cutoff.
  - **Use of PK & PD data for attributes:** How much other data like PK and PD data is used to justify attributes and how much is just a bioassay?
  - **Likelihood of Interactions:** This has been an issue in Europe, too – how much do you worry about interactions in terms of parameters, and impurities too? Because for biologics, impurities can interact with product. For instance, if you have a metal and a protease you might get protein degradation, but for each one alone, you could tolerate a lot.
independent. “The question we are asking is, ‘can you demonstrate that every single parameter in your process is site independent or size independent?’ Right now we don’t have any protocol or any demonstration of that.”

At the IFPAC regulatory forum, EMA’s Korakianiti commented on the design-space scale-up concern: “A problem that is troubling regulators at the moment is that the design space in most cases is developed at lab scale and pilot scale. How do we verify the validity of the design space at production scale?” she queried. “How do you give assurance that those conclusions are valid above pilot scale and during the life cycle of the product?”

FDA’s Kozlowski expressed a similar concern at IFPAC: “You know that space is good at lab scale. You don’t know how your experience at full scale will fit in.”

“The answer,” he suggested, “is really to do continuous modeling – multivariate statistical process control. Continue to learn about that space as you explore it, and that knowledge will help you really verify what you have shown in the models and gain experience.”

**QbD Puts Spotlight On Knowledge Management**

How the flow of quality-by-design knowledge from development into manufacturing and through the production lifecycle should be managed and regulated is a central concern on the industry/regulator table.

The concepts, use, and practice of knowledge management are being refined as industry and regulators progress along the QbD pathway. As more product and process knowledge is generated and submitted, both parties are being challenged with ensuring they have robust processes in place to appropriately capture and act on this knowledge.

In the QbD context, a key element of knowledge management “is really the conversion of the filing commitments into manufacturing instructions, controls, and material and product release specifications at the site,” AFSSAPS’ Ertle maintained at the PDA/EMA conference. “On the site,” she said, “we want to see how you are translating all of the knowledge you gained during development” into your manufacturing processes.

Ertle elaborated on what would be expected during inspections related to QbD submissions: “We would like to see the knowledge transfer process,” because “we want to make sure that all the knowledge you gain at the development site is really transferred to the manufacturing site.” If there is not a strong linkage between development and manufacturing, “all the work you have done unfortunately is lost.”

**The concern from regulators creates implementation questions for manufacturers.**

Addressing a quality systems interest group session at PDA’s 2009 annual meeting, Genentech Director of Corporate Quality Christa Hartmann addressed the need to communicate between manufacturing sites in addition to communicating from development to manufacturing (see Appendix V).

“If you think about a multisite manufacturing company like Genentech,” she said, “how do you get manufacturing information or technical information you learned during commercial manufacturing across the sites? How do you share best practices?”

Hartmann recommended leveraging existing solutions. “Knowledge management in the medical device industry is known as your ‘design history file,’” she explained. “It is how you designed that medical device. Why should we try to recreate the wheel here? How can we leverage that kind of model?” As an alternative, she suggested generating European-type product specification files.

**Regulators are also examining their internal processes for knowledge management – specifically the interface between assessors and inspectors.**

Speaking at the IFPAC QbD regulatory workshop, EMA’s Korakianiti noted that “as an agency, we need to bring down the silos” (see Appendix III).

“It is very important,” she stressed, “to improve the flow of information between assessors and inspectors…. There is a need for a very close collaboration and interaction” between them.

One action being taken in the EU is to revise the assessment reports. EMA has provided more internal guidance, creating “a kind of summary document at the end that could be transmitted to the inspectors. They can have a quick, very good understanding of the application” that is useful to them when conducting an inspection, Korakianiti noted. To further improve knowledge transfer, “usually when it is a pre-approval inspection, the inspectors are accompanied by an assessor.”

At the ISPE annual meeting, Q8-10 IWG member France pointed out that knowledge management is “not a new concept” and is always important regardless of the development approach.
The reason Q10 highlights knowledge management, he explained, is the expectation that more complex information generated by QbD and PAT real-time and control monitoring systems “will need to be better captured, managed and shared during the product life-cycle.” Q10, in turn, provides “a systematic approach to acquiring, analyzing, storing and disseminating information related to products, manufacturing processes and components.” Knowledge management, on the other hand, the IWG member clarified, is not a system but an implementation enabler for the concepts described in ICH Q8-10.

The Burden Of Knowledge

The problem with knowledge is that it begs to be acted on and those actions may draw regulatory scrutiny.

At the IFPAC panel session, CDER’s Kozlowski addressed the issue of pursuing knowledge and the possible consequences in the context of updating analytical methods.

He acknowledged that firms may feel disincented to update analytical methods since “it is expensive, and there is regulatory risk. I would call it undiscovered pre-existing variability. You use a better method, you have a peak you never saw before. It may have been there the whole time, but now the burden is on you to show that peak was there the whole time or doesn’t matter. That is a high risk in the regulatory world,” he pointed out.

“Good companies” characterize their processes well using the latest technologies, Kozlowski said. The problem is that when you do this characterization “you learn something new.” The question then becomes, “will somebody make you control it? Is there a penalty for knowledge?”

While regulators shouldn’t be punishing manufacturers for gaining more knowledge about their processes and methods, firms “should be doing that and using it,” he said. And once that knowledge is gained, it can’t be ignored by either the firm or the regulator. “If you know something matters,” Kozlowski emphasized, “you need to understand it and control it.”

The same theme is playing out in the application of quality by design to existing products.

“We are seeing some reluctance to identify CQAs for existing products due to concerns about creating misalignment with our registrations. Should we be concerned about this?” an audience member from industry asked the regulators on a panel at the ISPE annual meeting.

“I would hope that you would not be overly concerned about having a misalignment,” CDER’s Morefield responded. “I think it is always better to know what you are facing…. I think you can work with whatever the results are – whether you find that you have CQAs that you may need to develop controls for, or whether you find that you have current controls that are maybe more than you need” – that attributes you thought were critical are not. “I think those would be things that would be important for you to know and understand to have good control,” Morefield stated.

“I don’t think it is a good policy to put your head in the sand and not look at your products and understand them,” the FDA review official cautioned.

At the IFPAC regulatory session, EMA’s Korakianiti posited that the decision for a company to pursue quality-by-design principles for legacy products reflects their commitment to QbD.

“With regards to already authorized products,” Korakianiti noted, “it doesn’t have to do with whether it is a new application or not. It mostly has to do with the company’s strategy. What I see is if a company is committed to that approach…then sooner or later they will be focusing on legacy products as well.”

At the session, Novartis Executive Director James Cheney discussed his company’s commitment to quality by design and its positive experience with applying QbD to legacy products in particular.

“Novartis has submitted QbD on a legacy product that we currently have on the market,” Cheney commented. “We had a product that was having an issue in production. It wasn’t a huge issue, but we didn’t understand enough about a certain part of the process, so that is why we chose to do that particular product…. We figured it was a product we didn’t understand, and we had an opportunity to apply some of our best scientists in the QbD process.”

The experience helped prompt Novartis to institutionalize QbD for both new and existing products. “We have kind of a dual-track program where we are implementing QbD in development, but we also have a lifecycle management group that is looking at our currently marketed products to decide where we should apply QbD to some of those products, of course based on different criteria,” Cheney explained.

At the same session, Bayer Yakuhin Chairman Norikazu Eiki shared his firm’s experience in gaining approval for making a
change to a marketed product in which they moved from individual batch control to continuous release. “In our organization, this created confidence,” he explained. Eiki affirmed that the approval and institution of that change motivated his organization to move further down the QbD pathway.

The practical implications of the new Q8-10 life-cycle paradigm on knowledge management, legacy processes/products, process validation, and manufacturing change control are being targeted by PDA’s “Paradigm Change in Manufacturing Operations” (PCMO) initiative.

The PCMO initiative was launched by PDA in mid-2009 to complement ISPE’s PQLI effort, which has been focusing heavily on the product/process development and regulatory filing side. The PDA and ISPE groups have been communicating on how to ensure the initiatives are not duplicative.

PDA views PCMO as a driver for “the establishment of ‘best practice’ documents and/or training events in order to assist pharmaceutical manufacturers of Investigational Medicinal Products (IMPs) and commercial products in implementing the ICH guidelines” Q8-Q11.

PCMO has four primary objectives: • enable an innovative environment for continual improvement of products and systems • integrate science and technology into manufacturing practice • enhance manufacturing process robustness, risk-based decision making and knowledge management, and • foster communication among industry and regulatory authorities.

PDA plans to publish a series of white papers and technical reports as output from the PCMO effort aimed at furthering the dialogue between industry and regulators on these important topics.

Models Help Development and Submissions

The understanding of the potential uses and value of models in facilitating manufacturers’ development efforts and helping regulators understand their complex processes is growing.

The importance of using models as well as maintaining them was highlighted in ICH Q8. Models were recommended in the guideline, for example, as valuable tools in risk assessment, the control strategy, and design space determination and scale up.

At recent meetings, FDA and EU regulators have been discussing how to maximize the value of models in QbD submissions and across the product lifecycle.

At the ISPE annual meeting, ONDQA’s Morefield summarized why models are important: “Models provide a simplified description of a complex system, so they are useful in taking things that are difficult to describe and putting them in an understandable way.”

Morefield outlined the types of models that can contribute to the QbD effort and how they can be deployed (see box on p. 29). “Models can be useful in describing the effects of input parameters on output responses,” she said. In addition, they can facilitate faster process development and optimization, help understand process robustness, and make process predictions.

Along with aiding in process optimization, models can help explain complex processes to regulators. “You may want to use a model rather than trying to use a picture or a chart” to address the complexity, Morefield explained. For example, “if you have multiple critical parameters that interact, you may want to use an equation to describe your design space rather than just a list of process parameters.”

Addressing CDER’s growing experience with models at IFPAC, ONDQA Review Chemist Sharmista Chatterjee emphasized the importance of understanding the uncertainty they contain.
CDER’S ELAINE MOREFIELD ON USE OF MODELS IN IMPLEMENTING QBD

At the ISPE Annual Meeting in November, Elaine Morefield from the CDER Office of New Drug Quality Assessment (ONDQA) offered a regulatory perspective on the use of models in implementing QbD. Morefield explained the types of models available and how they can be used to enhance the development and submission process.

Why do you want to use a model? Models provide a simplified description of a complex system, so they are useful in taking things that are difficult to describe and putting them in an understandable way. Models can describe the effects of input parameters on output responses. They can facilitate faster process development and optimization. They can help understand process robustness, and they can make process predictions.

There is a decision pyramid that can be used to decide what kinds of models to have. They derive from trial and error experimentation. That is really the bottom of the knowledge pyramid, where you are just trying to find understanding and generate data. Then the next step can be decisions based on a univariate approach. I think typically a lot of our decisions on process parameters are developed based on univariate approaches currently. We are trying with quality by design to look into more DOE and multivariate approaches. The next level would be to understand the causal links and predict performance – so some understanding of how things are related. The next level is a mechanistic understanding, where you may have some understanding of what mechanisms are causing the responses from the input parameters. ‘First principles’ is the top of the knowledge pyramid, where you really understand what is happening and why, and you can predict.

Types of models: Models are broadly divided into two categories: You can have a quantitative model – that is, a mathematical representation of a system or phenomena. Or you can have a conceptual model – that is, a non-quantitative representation that describes how the input parameters are linked to output parameters.

Here are some examples of quantitative modeling methods: • You can have mechanistic models, which include things such as exact solution, finite element model (FEM), computational fluid dynamics (CFD), and discrete element model (DEM). • You can have empirical models that include things like regression models, chemometrics, neural networks, and in vitro/in vivo correlation (IVIVC) types of models that are empirical. • You can have semi-empirical models such as scale-up equations, where you have some understanding of the mechanisms but not full understanding. Property estimation is another type of semi-empirical model.

Models can be very useful in pharmaceutical development and manufacturing. They are useful to formulation development. IVIVC can be a very useful model to understand drug release and dissolution, but it is not always possible to obtain the IVIVC. Design space models can be used for process development. Mechanistic or empirical models can be used to optimize your process during your scale-up. Scale-up models can be used to develop your commercial scale process. On-line process control frequently uses models for chemometrics and other things. So, they are useful at every stage of development and manufacturing.

Models are very useful for quality-by-design approaches. They are useful for developing the design space. Risk analysis can use models. They are useful for gaining process understanding – using statistically designed experiments to get models of your processes and outputs. They are useful for optimizing the process and describing the design space. You may want to use a model rather than trying to use a picture or a chart – some things might be too complex. If you have multiple critical parameters that interact, you may want to use an equation to describe your design space rather than just a list of process parameters. Models are also useful in developing and implementing your control strategy. They are useful for controlling process performance and monitoring process and product quality for continual improvement.
“Any measurement has some uncertainty, and good understanding of that will tell us the limitations of the model and how the control strategy should be designed to prevent the associated risk. Risk depends a lot on what uncertainty is in the model.”

Chatterjee also stressed the importance of verifying models. Doing this verification “gives us an understanding of what the limitations are for the model, and how the control strategy should then be designed,” she said.

The ONDQA official stated that her office is willing to work closely with applicants prior to submission and during the review process regarding the use of models.

The use of models in regulatory submissions has also spawned questions and debate in the EU. Some of the key issues confronting regulators were highlighted by AFSSAPS’ Lina Ertle at the PDA/EMA October conference.

Models are generally initiated in product and process development at pilot scale and later transferred to manufacturing. “Those models are subject to lots of updates,” Ertle pointed out. This leads to regulator questions, specifically for multivariate data analyses, which are “very sensitive to variation.”

The questions include how the model should be represented in the regulatory submission and which version from the development/manufacturing cycle should be submitted. Also at issue are what level of detail should be submitted, which in part depends on what the regulators request, and what data should be available for review at the manufacturing site. As Ertle pointed out, the answers are “not clear now.”

The regulatory implications of the need to update models as process and product experience is gained is problematic. “How should we handle the model lifecycle – through change control or regulatory submission?” she quizzed.

Asking for a regulatory submission “with every update of a model would not be justified,” Ertle commented, as it would create a large amount of work for both the applicants and the regulators. The current discussion is around what should go into the dossier initially, and how model updates should be handled – what types of changes should trigger a regulatory submission.

Another concern facing regulators is the quality management system for handling of out-of-model/outlier/out-of-specification (OOS) results and when to revert to reference methods.

Ertle cited an example using content uniformity: “You have a model…based on NIR and it is predicting content uniformity. You have an out of specification coming from the NIR application. So how should you handle this? Are you going to reject the batch immediately or are you going to revert to the reference method?”

Most firms, she recognized, would run the reference method – likely HPLC. If the reference method confirms the OOS predicted by the model, then there is no issue. However, if the reference method shows the tablets meet specifications, most firms would release the batch. “I have no problem with that,” Ertle commented, “because the models are predictive models and we know that the models are very sensitive to variation in the process.”

However, Ertle emphasized that in the latter scenario, “our expectation as a regulator is that you use that information to investigate the models and to update the models, because…it means that your model is not robust enough and you need an update.” She recommended that each time an OOS occurs, manufacturers should consider investigating why the model did not capture it and whether model updating is needed.

QbD For Analytical Methods Having Strong Impact

As industry moves forward with quality by design for processes and products, including broader use of quality risk management and design space, the analytical methods that serve as a foundation supporting these facets are coming under more scrutiny by both industry and regulators.

Since entering the Q8-10 dialogue (IPQ, Sept./Oct. 2008, pp. 29-30), the application of QbD principles to help strengthen this analytical foundation has gained considerable traction.

Industry is now reporting significant payoffs from the programs that have been initiated in better understanding the sources of method variability and their implications for control of the product. The experience is also bringing into relief the questions that need to be addressed to realize the full potential that the application of QbD in the analytical arena has to offer.

Speaking at the IFPAC conference, GSK Analytical Services Director Jennifer McCafferty stressed the impact that implementing analytical method QbD (“AMQbD”) has had on her company’s lab operations.
“You can validate your analytical method, and the specs are big enough to drive a truck through, and your method will validate, and it will transfer, and it will work for a while,” McCafferty pointed out. However, that approach provides no built-in safety margin nor a true understanding that will ensure the method is robust. The robustness of methods is important, she stressed, especially when those methods get transferred “from lab to lab all over the world.”

Describing the evolving AMQbD program at his firm Novartis, Rosario LoBrutto also pointed to the importance of analytical method robustness. You can “live close to the edge of a cliff and everything is fine,” he said. However, when the method is transferred to technical operations, “you never know when you are going to fall off the cliff.”

The challenges of applying QbD in the lab are driving firms to re-think how they organize their work. LoBrutto explained how this process has unfolded at Novartis across the global corporation.

“All of our work is actually peer-reviewed in analytical strategy meetings,” he said. “We have members on this peer review team from across the globe.”

This cross-functional team includes members from technical, chemical and pharmaceutical operations, regulatory, and QA, who all participate in this review before any experimental work is done. Method validation is not performed until the robustness is complete. The team must be able to identify the critical method factors and explicitly state them in the method itself, as well as listing the critical method attributes identified. Further peer review of the risk assessment as well as management reviews are mandatory prior to proceeding with experimental work.

GSK’s McCafferty summarized the benefits seen at her firm for the IFPAC audience. “I think really the most important benefit that I have seen and that data exist for is more robust methods,” she stated.

When GSK began work in this area in 1998, 30% of the methods were judged robust, and another 50% were robust but had a lot of stringent controls such that there was little flexibility – they had to be run a certain way with no deviation. The result was that a lot of waste was created in the laboratory by unnecessary controls. At the time, 20% of GSK methods were judged not robust.

After AMQbD tools were developed and implemented, the number of robust methods went up to 66%. “We are now able to be more judicious and informed about which controls are needed, and where we can allow flexibility in the labs for efficiency and other reasons at the discretion of an analytical chemist who is trained in the lab,” McCafferty affirmed.

Other benefits include an increase in approved “right first time” with respect to analyst errors, conclusive investigations, improved lab flow, and a benefit to the manufacturing organization in terms of a scientific framework that allows more effective management of changes that deliver equivalent performance.

McCafferty emphasized that QbD enables “a more lifecycle approach to managing our methods [and] can allow change control without having to reproduce the data over and over in various labs around the world.”

GSK has also seen benefits from QbD in driving a consistent approach across new products and the institution of a one-team dynamic including cross-functional feedback loops.

“It is really the voice of the customer in the manufacturing labs hard-wired back into that design phase, so the R&D scientists know what it is that is needed for a robust method” in manufacturing. Important to these interactions, McCafferty stressed, is knowledge management and the use of GSK’s knowledge repository.

In addition to the benefits of QbD in developing analytical methods, there is also agreement that many older methods need to be examined and updated by applying the QbD toolbox.

During the discussion session at the IFPAC pre-conference regulatory workshop, CDER Office of Biotechnology Products’ Kozlowski commented on the implications of outdated methods and the need for more regulatory focus in this area.

“If you have a product that is three decades old, it may be analyzed the same way it was when it was approved.” FDA, however, has dealt with problems recently that better analytics would have forestalled, he stressed. “My sense is analytics really do need to get updated, especially in a world where there is counterfeiting.”

Application of QbD In Analytics Poses Some Issues

While the benefits of applying QbD to analytical methods are getting clearer, there are hurdles in the conversion process for those methods currently in place.
During the IFPAC pre-conference workshop, an audience member from industry cited the potential regulatory filing costs involved.

“...we get understanding and learning on an existing product where we can make a real change, and there is a prioritization, because it is extremely costly. We have examples where it costs a million dollars in fees to save the lab $300,000 in inefficient methods or improper methods. That is a real challenge.”

EMA’s Korakianiti commented that the new EU variations classification guideline which went into force at the beginning of this year introduces additional flexibility that may be helpful in the method change context, including the ability to “downgrade the changes.” She added there will be a revision to the fee regulation next year, and “possibly there will be further flexibility there connected with changes.”

Although challenges exist with applying AMQbD to small molecules, the task is more daunting for large molecules. The issue was discussed at the recent WCBP CMC Strategy Forum on higher order structure of proteins.

The forum explored the relationships between higher order structure and the quality of therapeutic proteins and peptides, vaccines, and blood-derived products. The understanding of these relationships plays an important role in defining and controlling the critical quality attributes of biopharmaceutical products. However, many current analytical methods for understanding the higher order structure of these molecules are either inadequate, costly, or unproven.

In his summary at the conclusion of the forum, Amgen Global Product Quality Executive Director Anthony Mire-Sluis underscored a key question regarding protein structure. “Do we know the correct structure? These products are always heterogeneous, so the question is, what is the right structure? Is there a right structure? Or do we just live with the fact that our proteins are heterogeneous?” With more sensitive analysis techniques and scientists learning more about the amount of variance, “are we going to end up burying ourselves in information that adds no value?” Mire-Sluis quered.

“...questions are being asked by both industry and regulators,” he said. “Many methods discussed give average results, so what is the meaningfulness of a technique that may miss very small amounts of change among a large amount of non-change?” He noted that this type of assessment would necessitate looking at a large number of batches.

Other concerns voiced at the forum include the relative inability of bioassays to predict bioavailability, PK, or immunogenicity. In addition, most bioassays have a variability of plus or minus 15%, and it is unclear if that is good enough. Although the use of NMR in determination of higher order protein structure was discussed, participants agreed that it will take more work for that technique to be useful and practical.

Mire-Sluis also pointed to the need for clarifying the term “sensitivity” for analytical methods. “Sensitivity is a word we really need to understand. We have heard it bandied around today, and it seems to have two meanings: One is the ability of the method to detect a very tiny change in all the molecules – versus the ability to detect a change in a very small proportion of the molecules that are in your sample. That is two completely different things.”

NIST Offers Help In Biotech Measurement Standards

The numerous measurement challenges of large molecules, including a lack of both measurement standards and appropriate tools, was a recurrent theme running through several of the WCBP conference sessions.

Along with higher order structure, the measurement and interpretation challenges involved with particulates and protein aggregates were among those receiving attention at the conference.

The lack of good measurement standards and tools in complex molecules has come to the attention of Congress, who asked the National Institute of Standards and Technology (NIST) to take a more active role in finding solutions. NIST is a non-regulatory agency in the US Department of Commerce, which has been involved in measurement science for several decades in support of many U.S. industries. NIST develops voluntary standards, but does not promulgate regulations.

In response to the Congressional request, NIST put together a proposal, released for public input in January, outlining areas related to biopharmaceutical analysis the institute views as needing improvement and how it could potentially contribute to addressing the needs.

Focal points of the NIST proposal include: • the need to ensure accuracy and comparability of the methods currently in use • a lack of precision and robustness in many existing methods • the highly variable, complex, and relatively
unpredictable nature of biological manufacturing processes due to a lack of tools to measure the internal workings of the cells being used, and • a lack of measurement infrastructure in place to help manufacturers and regulators easily identify the appropriate proteins emanating from the host production cells.

The proposal outlines potential action plans and tasks to assist in closing these gaps. In general, it calls for NIST to “develop and disseminate standards (reference methods, materials and data) and establish calibration/validation services to enable confidence in the measurements used to characterize and compare biopharmaceutical products.” This work, the proposal indicates, would be performed in collaboration with biopharmaceutical manufacturers, instrument vendors, academia, and other organizations such as FDA, USP or NIBSC.

Michael Amos, Biosciences Advisor to the Director of the Chemical Science and Technology Laboratory at NIST, explained the thrust of the proposal at a special session at the WCBP conference intended to promote discussion and feedback. Participants received the detailed proposal prior to the meeting.

“The program in a nutshell is to focus on three major areas,” Amos stated: “to develop the measurement resources and infrastructure to support the understanding of the sameness of biologic drugs made by different manufacturers or different processes; to improve the safety and efficacy of drugs; and to improve efficiency and reliability in manufacturing processes.”

“My colleagues,” he commented later, “are experts in measurements, but not necessarily the application and the real-world needs. We really need to be connected with industry at the hip, and we need to make sure anything we do is really relevant to what your needs are.”

Following Amos’ opening remarks, a discussion session was held to gather input and answer questions from both industry and regulators in the audience. Participants agreed on the desirability of reference standards to measure protein particulates and aggregates – an area cited in the NIST proposal.

“Protein standards for particulates and aggregates could be very useful,” an industry participant stressed. However, he cautioned that the effort would “bear a little bit of exploration, because I think this is deceptively complex. I would encourage you to seek a lot of scientific input. Aggregates and particulates may not be stable. If one thinks about a standard one hopes they will only need to make it once, or once every decade or two, as opposed to once every three months.” He added that this process will likely require some sort of development program to seek out materials that work as intended and are also stable once made and through shipment.

Another industry participant addressed the problem of how much reference standard would be needed. “When you are talking about making a standard, are you talking about making enough so all of us that are running these various methods can use them? Or are you talking about rolling out something that might help qualify instruments to use once a year or every six months? Because if you are talking about enough references to be used on a regular basis, then it really is an imposing task.”

NIST’s Michael Tarlov, who is chief of the process measurements division and spearheading the particulate/aggregate measurement part of the NIST effort, commented on the concerns raised regarding producing these standards and their stability.

In launching a pilot program in this area, NIST has been seeking input on whether standards are needed and if so what type, Tarlov explained. “What would they be used for? What exactly would they be? We have talked to different people, and we get different answers.”

The question of stability is still open, Tarlov said. “For the protein particle standards, we talked to some who said it would be too daunting to make them due to stability issues, and you would need to use some kind of surrogate. Others believe maybe you could make stable protein particulate standards.”

Also of consideration, he said, is how well defined the sizes should be, and whether they should be discrete sizes or just a fairly well characterized distribution. If the latter, he added, “we would want to have some kind of gold standard technique that we would be able to rigorously characterize that distribution to, compared to the methodologies that are currently available.”

As Tarlov’s team learns more from its initial interactions with industry and academia, “we realize it is not going to be an easy thing, but we think that we have to start some place on this.” He pointed to a general consensus from the discussions on subvisible particles and aggregates throughout the WCBP conference that protein particulate standards would be useful.
OBP Division of Therapeutic Proteins’ Kathy Lee expressed her enthusiasm for the particulate/aggregate standard-setting project and its usefulness in making regulatory judgments. Producing this type of standard, she emphasized, would facilitate comparison between the wide range of instruments currently in use.

“With a standard we could more easily understand the differences between the different instrumentation that is out there that people are using. Right now, because we do not have good standards, we cannot compare easily across instrumentation, especially when it comes to particulates. Even though we can measure them well, I do not know how meaningful it is to use data from different systems, currently, the way the paradigm is set up.”

CBER Medical Officer Malcolm Moos joined Lee in supporting the desirability of the standard-setting effort, counseling on which types of protein standards would be most useful.

“When you talk about a standard that allows us to compare, or others to compare, instrumentation and methods between and within laboratories, there is a strong rationale for perceiving an immediate utility.” However, Moos pointed out, “standard methods meant to apply across the board get into areas of complexity that can be awfully subtle and very product-specific.”

Proteins by their very nature vary from each other so much that it is important to consider their characteristics and to devise a method that will work for different proteins. “A standard method that might work for all proteins might be less valuable than a standard peptide mixture that could be used to evaluate different instrumentation platforms,” the CBER official pointed out.

The need for visible particle standards was also espoused during the discussion. It was pointed out that when examining product vials, different analysts see different sized particles, so having protein standards for different sizes of visible particles would be very useful.

An audience member who had attended the CMC Strategy Forum on higher-order structure of proteins commented that there was agreement among participants that it would be helpful to have more tools available for evaluating subtle changes in conformation of proteins. “I think more work on this would be appreciated by everyone, from early stage discovery molecules all the way through to commercial development,” he affirmed.

NIST official John Schiel commented on the institute’s ability to address the issue. “We do have capabilities to look at high resolution structural analysis of proteins and nucleic acids. We are thinking about methods such as NMR, IR, CD, and taking combinations of spectral signatures to get a better idea of how we can correlate those with structure and also dynamics. The precision at which we can do that, discriminate between subtle changes between the proteins, is still to be determined.”

Lilly Regulatory Advisor John Dougherty stressed the desirability of NIST cooperating with national measurement institutes in other countries to work toward harmonization of standards, as opposed to developing different standards in different countries.

At the conclusion of the session, NIST’s Amos commented that the input was valuable in helping NIST understand the needs of the industry and regulators and the challenges that lie ahead and how to prioritize the institute’s activities.

USP, PQRI Exploring Their Roles

USP is also stepping up its efforts to help apply better measurement science to pharmaceutical and biotech manufacturing in conjunction with NIST as well as other national metrology institutes and ISO.

To expand the pharmacopeia’s applied metrology capabilities and increase the interlinking with the other measurement standard setting organizations, USP brought on board from NIST William Koch to head its metrology effort (IPQ, Nov/Dec. 2008).

The importance of building the advances in measurement science into the regulatory framework was a key theme at both USP’s Fall 2008 and 2009 annual scientific meetings.

At the 2008 meeting, USP CEO Roger Williams stressed that the rapid advance in metrology is a significant force driving pharmacopeial evolution. He added that this advance has not emanated mainly “from either the regulatory agencies or the pharmacopeias, but rather more the national metrology institutes and ISO.”

Williams anticipated that USP and the other pharmacopeias as well as the regulatory agencies will be working increasingly closely with the national metrology institutes and their global parent body, the International Bureau of Weights and Measures (VIPM) located outside Paris, to solve the complex
challenges faced by modern measurement science. Involvement, he said, will likewise be increasing with ISO by virtue of their guidelines and other documentary standards.

A Fall 2009 USP white paper on the pharmacopoeia’s role in meeting the upcoming challenges in bio/pharma standard setting, harmonization and adulteration commented on the importance of applied measurement science and suggested roles USP can play in that arena. Among these is the creation of Certified Reference Materials. CRMs allow manufacturers, regulators, and others to compare results across different procedures (see box below). Four USP reference standards now have “certified” status.

The white paper was one of a formative series that USP issued during the Fall to highlight the needs and help set the agenda for the next several years. USP will hold its “2010 Convention Meeting” in April in Washington, D.C., which will further define the pharmacopeial agenda for the next five years.

Another key forum providing implementation support for the evolving ICH Q8-10 paradigm is the Product Quality Research Institute (PQRI). PQRI has played a pivotal role in defining emerging quality issues and laying the groundwork for forward-looking regulatory responses.

The non-profit volunteer consortium was established in the late 1990s to help bolster the effort by CDER’s Office of Pharmaceutical Science (OPS) to strengthen the scientific foundation for pharmaceutical regulation. Roger Williams, then OPS director, spearheaded its creation.

PQRI brings together industry, regulator and academic experts “to generate and share timely, relevant, and impactful information that advances drug product quality and development.” Its mission is to provide a forum for working cooperatively to “conduct research, exchange information, and propose methodology or guidance to pharmaceutical companies, regulators and standard-setting organizations.”

PQRI’s supporting organizations include the American Association of Pharmaceutical Scientists (AAPS), which provides technical/administrative support for PQRI at its Arlington, Virginia headquarters, the Consumer Healthcare Products Association (CHPA), the International Pharmaceutical Excipients Council (IPEC), the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), FDA and Health Canada.

PQRI has a Board of Directors and a Steering Committee that sets goals for the institute and oversees the projects conducted by three Technical Committees – covering development, manufacturing and biopharmaceutics – and their respective working groups.

The focus of the Development Technical Committee (DTC) is on research projects that “help to more clearly define, through technical examples and applications, QbD concepts.”

A combination of the former Drug Product and Drug Substances Technical Committees, the DTC has ongoing working groups focused on stability shelf life, container/closure systems, sulfonate esters, and thresholds and best practices for leachables and extractables in parenteral and ophthalmic drug products.

In the Fall of 2006, PQRI published an extensive report on thresholds/practices for extractables and leachables (E&L) in orally inhaled and nasal drug products (OINDP) and held a series of training courses on the recommendations. The E&L initiative for parenterals and ophthalmics was subsequently launched to build on the work done in the OINDP area.

[Editor’s Note: The March/April 2008 issue of IPQ provides an in-depth analysis of PQRI’s contributions, as well as those of other organizations including IPAC-RS, the
The DTC Stability Shelf Life Work Group was established in late 2006 to investigate current and alternative statistical methods for estimating the shelf life of pharmaceuticals from stability data. PQRI explains that the group was formed under the premise that the QbD initiatives “may have implications for the current approaches to establishing shelf life, and that a contemporary consideration of this problem was warranted.”

The objectives of the group are to extend the knowledge base for evaluating stability data, and propose best practices and statistical methods for estimating shelf life consistent with FDA’s QbD initiative.

One of the two main focal points of the stability working group is to better define “shelf-life,” and a publication on that topic is being prepared. The group is also working on developing and evaluating alternative shelf-life methodology that is predictive of future batch performance. Among the approaches under consideration is a coupling of quantile regression and calibration techniques. At the PQRI December conference, Michelle Quinlan, who has been doing research on this approach at the University of Nebraska-Lincoln in conjunction with PQRI, updated the participants on her progress in confirming its validity.

PQRI’s sulfonate esters initiative relates to the growing concern at EMA and FDA with genotoxic impurities within drug substances and the threshold of toxicological concern (TTC) concept built into recent EMA and FDA guidelines.

The PQRI working group conducted research studies to first develop highly sensitive analytical test methods to detect sulfonic acid esters and then employ the methods to study the stability of these compounds under varying conditions, including pH and water content.

Basically, the working group showed that sulfonic esters do form under extreme manufacturing conditions, but that the conditions can be manipulated to prevent or minimize their creation. The project was successful in providing regulators and manufacturers a better understanding of the chemistry of the molecules and of how to manage and evaluate the issues involved.

PQRI has made important contributions in a variety of other areas under DTC purview, including blend uniformity testing, RFID, excipient control strategies, moisture vapor transmission rates for container/closures, mass balance measurement in OINDP cascade impactor testing, and HPLC column comparison. Other areas of DTC focus include particle size analysis/specification-setting and downstream API manufacturing changes.

PQRI’s Manufacturing Technical Committee (MTC) also defines its mission in terms of providing support for the ICH Q8-10 paradigm: to help develop “science-based approaches that appropriately integrate risk assessment and will encourage innovation and continuous quality improvement in pharmaceutical manufacturing and flexibility in the associated regulatory processes.”

Among MTC working group achievements have been recommendations incorporated by FDA in finalizing its aseptic processing guideline, followed in 2007 by recommendations to the agency on post-approval changes for sterile products.

MTC work is ongoing in developing risk management (RM) case studies and assessing risk models from development through manufacturing, and a white paper has been published in applying RM to solid dosage form manufacturing. A PQRI survey was conducted and published assessing FDA Team Biologics inspections, and further work is targeted on biological indicators in isolator systems and specification design/lifecycle management. A white paper has also been published on process robustness for oral solid dosage forms.

In addition to its ongoing projects, PQRI is considering how it can contribute to meeting the challenges in four areas that are currently emerging into high relief in the regulatory landscape: • nanoparticles • complex dosage forms • biosimilars, and • supply chain integrity.

PQRI held a conference in mid-December to help chart its course. Pointing to the “vastness” of these areas in his introduction at the conference, PQRI Steering Committee Vice Chair Anthony DeStefano (USP) explained that “it is not our intention to be all encompassing. But I think it is important that we develop niches that we feel we can operate beneficially in.”

At the conference, presentations were given by industry and regulator experts followed by breakout sessions to draw
input from participants on each of the four areas on the PQRI radar screen.

Among the presenters was CDER OPS Research Policy Associate Director Nakissa Sadrieh who addressed emerging regulatory considerations for nanotechnology-containing therapeutics (see Appendix IV).

Sadrieh discussed how nanotechnology is defined, why nanoparticles are being used, FDA’s action on nanotechnology, quality assessment and safety considerations for CDER products, and concerns and initiatives in developing a regulatory framework. Sadrieh is chair of CDER’s Nanotechnology Working Group and has been actively involved in PQRI activities.

‘What, I guess, we don’t know right now is, for the type of nanoparticle that we may be looking at,” for example, a dendrimer or nanotube, “what are going to be the important properties that we need to know [and] what is the best way for us to be able to evaluate those properties?” she said. Pointing the way toward a potential PQRI project, Sadrieh added that “if somebody could actually generate a table with the particle, the property and the methods that one would use to actually evaluate or characterize, that would be a great help to be able to adequately review these products and to know whether there are issues that we need to look at or not.”

Another area of concern, she added, is that the properties of nanoparticles may be “quite different from the normal properties that we look at right now for small molecules, [e.g.] electron microscopy methods. These are not methods that have been used in the past in manufacturing. So we need to find ways of being able to identify methods that are going to be adaptable to be able to actually develop drugs.”

One of the efforts CDER is making in developing a regulatory framework for nanotechnology-containing drugs, Sadrieh stressed, is trying to identify which approved products already contain nanoscale materials to see if there are any linkages between the particle size and problems such as adverse events or toxicity. Particle size has not been a focal point in application review and nanotechnology has not been specifically defined by FDA in this context. Thus far, FDA has not felt the need to develop specific policies for nanomaterial-containing products, although “in the future that is something that may be necessary,” she explained.

An agency-wide guidance is being developed on nanoscale materials in FDA-regulated products, which will specify that sponsors need to tell FDA when their products contain them. CDER is also finished drafting a MAPP directing reviewers to identify applications containing nanomaterials to help with agency tracking of related information.

CDER is also involved in research to understand better the properties of nanoparticles in CDER-regulated products that require adequate characterization. “We will try to understand the instrumentation that does best to characterize nanoparticles in CDER-regulated products,” Sadrieh said. CDER has been evaluating, for example, whether there is dermal penetration of things such as titanium dioxide in sunscreens, and the results indicate not, she noted. She added that the center is “using the nanotechnology database under construction to identify additional gaps that may require a policy.”

In the breakout group discussions on where PQRI could play a role in the nanoparticle arena, participants picked up on some of the gaps identified by Sadrieh, including definitions, patient risk with nanoparticles, and the adequacy of analytical methods.

The breakout participants stressed the need to perform a “landscaping” exercise that would involve learning from other industries that are using nanotechnologies and identifying where the gaps and issues lie for drugs. The need for developing standards for nanotechnology testing was also highlighted, with participants recognizing the potential issues with comparing assays that may be different from organization to organization. The recommendation was also made that regulator concerns should be identified up front as a mechanism for narrowing where PQRI can help.

The complex dosage form breakout groups similarly pointed to the need for baseline issues to be elucidated, including the need for a good definition of complex dosage forms and categorization of which products are included. It was pointed out that the aspects common to these products include complexity, manufacturing difficulty, and delivery issues, as well as the challenges of drawing in vitro/in vivo correlations.

The participants suggested that there are risk criteria that the FDA can help clarify by providing relevant data – for example, on recalls, batch failures, adverse events and dosage forms that present particular manufacturing problems. It was recommended that the agency be asked where a PQRI working group might add the most value in this area.
Noting that the Scale-Up and Post-Approval Changes (SUPAC) guidances were developed without the benefit of QbD and DOE concepts, the complex dosage form breakout participants suggested that there may be an opportunity to use a complex dosage form such as transdermals as a test case for SUPAC updating. It was pointed out that although there is a white paper describing change pathways for transdermal delivery systems, there is no approved guidance.

PQRI projects have already encompassed issues around aseptic, bulk active and packaging post-approval changes. In turn, the potential for PQRI to contribute further to a follow-up SUPAC-like effort to refine manufacturing change policies in view of the new quality regulatory principles was a recurrent theme through all four of the breakout discussions.

The need for developing more coherent manufacturing change approaches for biotech products, in particular, was stressed in the biosimilars breakout groups as an important link in helping solve the regulatory issues involved.

It was suggested that PQRI engagement in the biosimilars area should encompass learning from the experience of biologic innovator companies in establishing comparability for their products following manufacturing changes.

In considering a general framework for developing bioequivalence criteria, breakout participants were not sure, given the fundamental differences between small and large molecules, that a broad criteria could apply. They noted that although two large molecules may be identical in their primary structure, there can be differences in secondary and tertiary structures that can change functionally, and sometimes small changes can have big impacts.

In this context, it was suggested that one way to establish high level criteria may be to first look at individual case studies in the EU and comparability exercises, then examine that data for similarities. At that point it might be possible to tease out several general areas for testing that would be required, which would begin to form a broad framework upon which some type of values could be built.

The breakout groups focusing on the supply chain noted that much work is already being done in this area by a number of organizations, and one of the challenges was to determine where PQRI’s expertise would best complement these existing efforts.

Suggestions included: • assessing “fingerprinting” methods from a technical standpoint to determine applicability and limitations of these methods • examining ways to improve security of certificates of analysis to prevent or detect forgery • identifying targets for “economically motivated adulteration” • creating a PQRI “standing group” that keeps informed on supply chain issues and is able to respond quickly to technical issues, and • helping pharmacopoeias update older monographs to improve the analytical methods they contain.

PQRI will be sponsoring a workshop on “addressing the role of pharmacokinetics in establishing bioequivalence for orally inhaled drug products” in conjunction with this year’s annual Respiratory Drug Delivery (RDD) conference in Orlando, Florida in late April. The PQRI workshop will include a series of case studies using the PK approach followed by breakout sessions with focused discussions on selected topics.

QbD Gaining Traction In Non-ICH Countries

Most large pharmaceutical companies operate globally and face challenges with differing product registration requirements in multiple markets. ICH continues to make strides in harmonizing requirements in the US, EU, and Japan, and globally through its Global Cooperation Group. However, countries outside ICH may continue to pose registration challenges.

At the IFPAC QbD/PAT regulatory forum, participants noted that they are making inroads with QbD in these countries, in part by defining “quality by design” in terms of the science behind it.

Novartis’ Cheney discussed his experience when requested by the State Food and Drug Administration (SFDA) in China to deliver quality-by-design training to their inspectorate. “They didn’t have a good idea what QbD was,” he recounted.

After the training session, Cheney spent some time with SFDA management, who he said also was not familiar with QbD. However, when he posed the question, “do you understand good science and engineering?” and asked if they would accept that in their applications, they affirmed they would.

Pfizer Executive Director Robert Baum, also present on that trip, commented that, “while I think some of the leaders of the SFDA understand what is going on, they are very quick
to acknowledge that [their] reviewers are not ready for this yet. They are still working on gaining an understanding of the initial series of the baseline ICH guidelines.”

Echoing Cheney, Baum acknowledged the confusion that may be caused by QbD terminology. “I wouldn’t call it a quality-by-design submission,” he recommended. “You are filing an application in that country, and depending upon the knowledge, science, and understanding” you put into the application, there is a reasonable chance you will get some flexibility from the regulators.

Bayer Yakuhin Chairman Norikazu Eiki maintained that there is still a lack of understanding even in Japan.

Eiki explained that many of the pieces that support QbD, such as the factors behind process understanding, “we have recognized in our society.” However, he added, “QbD is not well recognized” among the top tier of Japanese pharmaceutical companies. Nor do the Japanese regulators, “especially PMDA and the Ministry of Health,” fully recognize or understand QbD and PAT and the value those approaches can add, he said.

GSK Pharma Launch and Global Supply VP Gordon Muirhead offered a different take on the QbD communication problem, suggesting the need for demystifying the term.

“Every time any of my colleagues asks me, let’s not do QbD, or let’s do QbD light,” he said, “I get them to say the words out in full. It is ‘quality by design.’ Which part are we not going to do? Which part are we going light on? Are we going light on the quality, or are we going light on the design?”

The bottom line, Muirfield suggested, is that “we are all scientists and engineers in here. We will have to justify that to ourselves before we justify it” to the regulators.

FDA’s Nasr added a note of optimism: “I think that there is a great opportunity in some of these developing countries. The reason for my optimism” is that “they don’t have old-fashioned regulatory or development approaches that they have to change and reverse. In some cases they won’t have anything.” Nasr suggested it could be more difficult to change existing regulatory structures than to help teach and build new ones, pointing out that in these cases the newer agencies could “start fresh.”

IPQ wishes to thank the following sponsors

---

IPQ wishes to thank the following sponsors

---

BioTech Logic
Manufacturing and CMC Consulting

CMC biologics

West
WestNovaPure.com

David Begg Associates
An NSF International Company
Component quality is increasingly important for manufacturing and processing drugs efficiently and problem-free. West’s NovaPure components deliver the ultimate in value and quality...by design.

- Reduce costly, time-consuming laboratory testing
- Mitigate the expense and exposure to regulatory risk of component sterilization and microbiological testing
- Reduce end-of-line rejections
- Complements Quality by Design initiatives
- Reduce the risk of leachables in the drug solution
- Helps achieve 2μm–10μm specification for subvisible particles in finished drug products
- Mitigate the expense and exposure to regulatory risk of component sterilization and microbiological testing
- Reduce end-of-line rejections

The packaging components you choose should mitigate the risks associated with injectable drug manufacturing. Call a West representative and ask about West NovaPure components. West NovaPure components deliver the ultimate in quality...by design.

WestNovaPure.com

101 Gordon Drive
Lionville, PA 19341
610-594-2900
800-345-9800

NovaPure™ and West and the diamond logo are trademarks of West Pharmaceutical Services, Inc. in the United States and other jurisdictions.

Copyright ©2010 West Pharmaceutical Services, Inc.
Keeping the balance...

between cost, quality and operational effectiveness in a global business.

Consultancy | Training | Auditing
Learn more about our range of GMP services at www.DBA-global.com.
At a QbD/PAT regulatory workshop preceding the IFPAC 2010 conference in early February, CDER Office of New Drug Quality Assessment (ONDQA) Acting Deputy Director Christine Moore gave a presentation on the “progress and challenges” in her office’s implementation of QbD. Focusing mainly on the small molecule arena (see Appendix II for a CDER biotech QbD review), Moore discussed the history of FDA quality initiatives, the ONDQA CMC pilot program, experiences since the pilot program ended, regulatory flexibility, recent QbD learnings, and future challenges for QbD implementation.

My talk today is kind of like a Dickens Christmas Carol on QbD and PAT – it is QbD past, present, and future. I am going to do a brief overview of where FDA has been on quality initiatives, where we have been in terms of the CMC pilot program, and where we are as far as what we have learned from our experiences….

Much of this started back in 2004 – even before that – with the FDA quality initiatives. We now call them the ‘21st Century’ initiatives. I think what is interesting is that really our focus has not changed over the past five or six years.

You look at what those objectives are, and you will see these are still the things we are talking about today, and that we have put guidances forward that we are incorporating in our day to day operations: • early adoption of new technological advances in the pharmaceutical industry – isn’t that what we are here for this week? • facilitate industry application of modern quality management techniques, including quality systems – okay, that is Q9 and Q10 • encourage implementation of risk-based approaches • then the last two objectives have to do with how we do our work [review, compliance and inspection policies based on state-of-the-art science, and enhanced consistency and coordination of FDA’s drug quality regulatory program]. And some of those changes we have made already. Some of them we are continuing to make within the agency.

So, what kind of guidances have we put forward, both through FDA and in the international community? Much of it started back in September of 2004 with the PAT guidance. That was followed by such things as the quality systems guidance, and, more recently, a draft guidance revision of the process validation to be more consistent with some of these new approaches to quality.

On the ICH side, we have: Q8, which was later revised to Q8(R), in 2005 and 2008; Q9 on quality risk management; Q10 on pharmaceutical quality systems. Recently – I would encourage you to look at these if you haven’t already – there have been some other documents published: the Quality Implementation Working Group Q&As to clarify some of the outstanding questions and issues regarding these current documents.

So, when you put this all on a timeline, you can see we have been pretty busy over these last five or six years. The speed at which things have changed within the FDA – sometimes when I sit back it kind of amazes me…. Now we have all of these guidances over the last five years – things that can fundamentally lay a new framework to change how pharmaceutical quality is being looked at.

The initiatives that are still ongoing include ICH Q11 on drug substances, and again continued efforts through the ICH IWG.
ONDQA CMC Pilot Program Results

One thing that I want to focus on here is the ONDQA CMC Pilot Program, which started in 2005 and has wrapped up. The objectives of this program were to offer opportunities for both industry and FDA to get experience with quality-by-design applications – what it means to put one together, how do we review it, how do we look at implementing some of these new concepts into application review. At this date, the pilot program is over. We have no current open applications for the pilot program. There were nine original NDAs submitted, and two supplements – one that was split into two parts, sort of, and ended up being three – accepted into the program. Eleven of them were approved, one of them was withdrawn for non-CMC reasons.

We are in preparation of a white paper we want to put together and distribute to industry and everyone as a whole, so that we can discuss what we have learned from that and document that.

What did we learn? A very short summary of the pilot program: This provided critical experience, I think, both to the agency and to industry about what it means to implement quality by design. We looked at some of the elements of quality by design in submissions, such as risk assessment, design spaces, proposals for regulatory flexibility based upon that enhanced science understanding. It allowed us to enable risk-based decisions based on the science that was presented in the applications. Much of what we learned was incorporated into these ICH documents. It is not just FDA that incorporated these ideas. These ideas were brought forward by industry as well, who also learned by going through this process.

With the pilot program being over, it doesn’t mean at all the QbD is over. We have many more applications outside of the pilot program, and I will go into that shortly.

I want to focus a little bit more on what we learned and how these ideas went into Q8(R). One of the things that kind of evolved as we looked at multiple applications is just an example of how one could put together a QbD-based submission. That is outlined in the steps of the Q8(R) document. Often times it starts with targeting the product profile, knowing what you want to make and how it is going to work, and determining what aspects in that product are critical to patient safety, efficacy, etc. Then understanding what aspects of my raw materials and process parameters affect those critical quality attributes that deliver the intended benefit to the patient. That is often done through risk assessment.

A design space can be developed, which is a quantitative model that shows how those inputs relate to those outputs. Then all of that can get molded into a control strategy for your manufacturing. QbD does not stop right at the point of where you put your submission together and get ready to launch your product. One of the things we have learned is that continual improvement, managing over the product lifecycle, is very important.

When you look at these three aspects, pharmaceutical development, quality risk management, and pharmaceutical quality systems as described in the ICH guidelines, what we found is that pharmaceutical quality rests on these. That was a learning for us. I think, myself anyway, I went into the pilot program saying we are going to get more information on the application. That is nice, but what I didn’t anticipate, and I think the community as a whole has come to understand, is that these three factors really have to work together hand in hand to ensure pharmaceutical quality. You have to have good product and process understanding, you have to understand what the risks of your product are and control them, and you have to have the implementation systems in place through your quality systems.

ONDQA Experiences Outside the Pilot

So what are our recent QbD experiences outside of the CMC pilot program? We have definitely seen an increase in the number of QbD meetings and applications. I did a count of how many applications we have had over the last two years outside of the pilot program that have QbD elements in them. Similarly if we were to count the ones that had not had a full-blown QbD treatment, the numbers would be much smaller. But even just companies incorporating some of those elements of QbD is a step forward.

ONDQA Experiences Outside the Pilot
It is somewhat of a subjective count [but] these are the numbers we came up with for 2008 and 2009: 12 NDAs, 18 INDs, meaning packages where they are talking about future NDAs, and six supplements for legacy products in which they introduced... QbD concepts. What I want to point out here is the number of applications that we have seen outside of the pilot now exceeds those that were in the pilot. I expect this number to keep growing.

Just as we are growing in terms of the number of applications, we are also expanding in terms of the challenges that industry presents to us, because the concepts and approaches are continuing to evolve. We have seen some fairly challenging regulatory approaches that have made us sit back and say, ‘hmmm, I have never thought about that before. How are we going to approach that’? We have gotten a good amount of reviewer experience in many areas, and we are starting to coalesce our review approaches, so we are both learning and we are continuing to learn.

Discussions Regarding Regulatory Flexibility

What are some of the discussions that we recently had for regulatory flexibility? I am saying these are discussions. I am not saying we have any answers at this time, but things that industry are bringing forward and challenging our thought processes with.

One we were familiar with from the pilot was design space for material attributes and process parameters. One that is still developing is real-time release testing approaches – things such as in-process tests in lieu of end-product tests, and surrogate models for dissolution testing, where instead of doing dissolution tests for every batch, you are using a combination of process parameters and material attributes, or process performance criteria, to link to what that measured value would be. Design space for analytical methods is one I know industry is very interested about. I co-chaired a breakout session at a biologics conference last week regarding that. Even topics such as starting material reduction of stability data upon site transfer have been discussed in the context of QbD.

As I mention, we don’t necessarily have answers for all of these topics, but we are considering them. We hold these discussions on a case-by-case basis. So if you or the other people in your firms have some concepts you want to bring forward, I would say definitely come talk to us and go through the standard meeting request protocols.

Recent QbD Learnings

I also mentioned that we have coalesced some of our thought processes and our learning regarding QbD applications. One of the topics that I think we are coming to good grips on is what good scientific practices there are for developing and maintaining NIR models. We also have a fair amount of experience on what good mathematical practices are for developing and verifying models.

We also have a fair amount of experience regarding what we like to see in terms of the application and the content submission.... I am not going to go into the details of this now. Some of you know what our preferences are – they ended up being in the ICH Q8(R) documents – and we have talked about them at other regulatory conferences.

I did mention that I would be linking this to scientific gaps, because even though we are on this road to implement QbD, we are not fully there yet. Some of the gaps we have are understanding that link between what that product is and how it works in the patient – that is, integrating the field of biopharmaceutics into QbD. We have had recently many conferences talking about this area.

Understanding complex products and processes we are still learning on, and Steve Kozlowski talked about the biotech products [see Appendix II]. We have similar complexities in terms of complex products such as transdermal patches. Another variant which has the statisticians talking is uncertainty in design space, and how you can use modeling and statistical approaches to understand how good is this design space. Steve touched on this as well, with the Bayesian methods for design space determination....
Modern control strategies: What kind of instrumentation and controls, how do you look at model maintenance and improvement, and how do you do continual process improvement to do the implementation of these quality-by-design concepts?

To break these out in a little more detail, there are issues regarding: translating process understanding into effective controls through on-line and at-line methods; effective sampling strategies; feed-back and feed-forward controls; applying modern manufacturing approaches, looking to get to where many other industries are; using lean manufacturing, real time release test approaches, and continuous manufacturing.

Continual improvement – how do you continually update your product and your process such that you are assuring product quality over time? Especially when you are talking about process analytical systems, models that you are using, and just the whole matter of knowledge retention, etc.

I have an example here that I think I put together about three years ago for an ISPE presentation (see diagram on p. 13). At that time I considered it a relatively conceptual example of where you could have a continuous manufacturing process with full automated testing and whatever.

The process is relatively straight-forward: your receiving, continuous monitor of a roller compactor for continuous granulation, another blending operation for lubrication, tableting compression, film coating, perhaps a spray system. And then you have various measurements along the way. All of that could then be tied in to a product assay for some of the more difficult measurements, such as dissolution testing. At the end of it you could integrate all of that information through statistical process control or perhaps, better yet, multivariate statistical process control. And whereas this seemed rather conceptual three years ago, I don’t think it is conceptual anymore, because I have seen over those last three years several presentations by both industry and academia that are putting practically every aspect of what is presented here in this so-called conceptual realm into practice.

So, where are we right now with this Christmas Carol story of QbD? I think the future is now. I think that we have the tools and the background to put all of these concepts together and move them forward. The FDA has put out quality initiatives to enable that fundamental paradigm shift in pharmaceutical manufacturing, where we have quality control strategies that are based on product knowledge and process understanding in a truly scientific and risk-based approach for regulatory oversight. Much of that science base is already in place, and we are going to see much of that this week. We have already obtained the groundwork of regulatory experience, and we are going to be continuing to gain that experience. But most of all, conferences like this and the opportunity for us to talk and have this continued dialogue will only help advance and move these concepts forward.
You Can Count On Our Expertise To Realize Your Goals.

We help put your plan in motion…

And then we finish it with you.

Our unique focus is helping you meet your development and commercialization needs by bringing your product to market quickly and successfully, while maximizing the expertise and resources you already have on board. With decades of experience and involvement in dozens of products that have been filed and approved in the United States and across the globe, we’re the experts you need to shape and execute your biopharmaceutical manufacturing and CMC needs.

Our approach is tailored to meet the requirements of your project. We can integrate into your development efforts, augment your team resources, or provide hands-on support. Our areas of expertise include:

* Process Validation
* Regulatory Submissions
* Quality Assurance

Our success has been our ability to serve as your technical expert and be the additional resource that helps you drive and execute your plan.

Contact us for the resources to start delivering on your goals.

Peter Dellva: (847) 730-3475
pdellva@biotechlogic.com

Or Visit:
www.biotechlogic.com
www.processvalidation.com

BioTechLogic®
Manufacturing and CMC Consulting
At a QbD/PAT regulatory workshop preceding the IFPAC 2010 conference in early February, CDER Office of Biotechnology Products (OPB) Director Steven Kozlowski offered a regulatory perspective on implementing QbD in the biotech context (see Appendix I for a CDER drug QbD review). Kozlowski discussed the importance of learning from experiences with small molecules, the CMC Biotech Working Group’s A-MAb case study, and the OBP pilot. His discussion of considerations that have arisen during the biotech QbD pilot on design space and risk assessment is provided on p. 27.

I am going to talk a little bit about what is going on for QbD implementation for biologicals.

One very important thing is to learn from what is going on in the small molecule world. There is a lot of information from the ONDQA pilot (see Appendix I) and from application experience with QbD and global experience that can help us with complicated molecules. Clearly the ICH guidelines can help with implementing QbD and its principles as applied to biotech and biological products, and Q11 will talk about both small molecule and large molecule drug substances.

Our staff is new to QbD as many reviewers are, so they are participating in conferences, forums, and training on QbD. Most recently, we had design-of-experiments (DOE) training for a large fraction of our reviewers. There are mock case studies and a pilot to look at QbD applications for biologicals. So those are the two things I want to talk about very briefly.

A-MAb Case Study

Mock case studies: EFPIA is drafting a monoclonal antibody mock case study. Very recently, in October of ’09, an industry CMC Biotech Working Group published a QbD case study about ‘A-MAb.’ It involved seven large companies, or large companies for bio, and some large companies in both. It is long, 278 pages, a lot longer than the ACE (small molecule) case study [see IPQ, Sept./Oct. 2008] and other ones. But there is a lot of meat in the case study and a lot of real data, some of which was taken from the companies’ own experience, to think about.

A-MAb is not a template for a QbD submission. It is not a definitive source of regulatory definitions and terminologies. There is terminology used in A-MAb that I don’t think comes out of ICH and can be a little bit confusing. It is certainly not the final science involved in how to approach biotech QbD. However it can be a source of challenging and very well thought-out examples, and provides the basis for many discussions and forums to contribute to QbD implementation for complex molecules. It was a very large effort by Ken Seamon [former FDA official and now Cambridge University professor] and John Berridge [former Pfizer official and ICH Q8 expert working group member] and really top scientific talent from a bunch of companies. So I think it is a very useful advance.

[Dealing with the many attributes in biologics] presents a real challenge. A-MAb has a number of tools to think about [including] a risk ranking and filtering tool, which is based on severity equals impact times uncertainty. Process capability was entirely left out of this. So it really was: would this oxidation affect quality no matter how often it occurs in the manufacturing process? And how certain are we that this oxidation would or would not do that?
There was another tool for this, a somewhat different methodology, and there was a third tool for non-bioactive impurities. If you have some impurity, there is probably a lot simpler way of deciding whether or not it meets the threshold of being a CQA.

Now clearly, as we have heard about many times, one then looks at the process for each of these attributes, decides what is important by some form of risk assessment, then ultimately translates that to experiments, which lead to optimizing what parameters matter, and then finally some sort of map of what matters, which evolves into the design space.

One of the challenges with the design space is what is in it. We have heard about what happens to critical process parameters. Does it include process parameters that are not critical? An example based on the A-MAb experience is...classifying process parameters into general, key, and critical. So ‘key’ is like in the PDA [Technical Report #42] – it impacts yield, it actually doesn’t impact quality. ‘Critical’ impacts quality, and ‘general’ doesn’t impact either.

Say you take an attribute like temperature, and you study it between 18˚ and 22˚ C. It doesn’t affect yield. It doesn’t affect quality. It is non-critical. Now you study it between 15˚ and 25˚ C. Suddenly your yield goes down a little at an extreme. Now it is key. Suppose you study it between 5˚ and 40˚ C, and at 40˚ you have degradation, now it is critical. One interesting challenge is that you can have a design space with nothing critical, if you make it small enough. You can have a design space where almost everything is critical if you explore a very broad knowledge space. So it seems a little arbitrary, for instance, to have no limits on your design space, if you study very little. There is a real challenge here to think about what is in a design space. I don’t have an answer – there aren’t answers for a lot of these things.

A-MAb brought up some thoughts about design space. [It includes a diagram of] a design space based on two glycosylation features of an antibody – the absence of fucose and the amount of galactose on the sugar tree…. They did some statistics, used a method called ‘Bayesian reliability’ (but there are a variety of methods one might use) to say: ‘We don’t want our design space to have a high probability if you are near the edge of failing. We want some extra level of assurance in our design space.’

So I throw that out as an interesting question. Depending on the statistics and the certainty you expect of your design space, it could be bigger or smaller. As regulators, we need to be able to understand the difference between a design space with no built-in margin of safety and one that has it, and really treat applications in a similar way.

[There is] a concept called an engineering design space…. Certainly as you scale up certain things, like bioreactors, it is very hard to keep all your variables the same – things like agitation – and how you would translate that, whether it is power, whether it is some other measurement. And as you scale up you may need to change variables. So how do you create an engineering design space to allow for that? Again, A-MAb didn’t have definitive answers, but it brought up potential ideas.

You do look across your experience at multiple scales and designs, and they suggest – which is something I think regulators will really need to think about – that if you can truly understand the micro-environment, then the engineering parameters of the bioreactor don’t matter. What really matters is what happens in the cell that is manufacturing the protein. But I think to feel comfortable with the right measurements in the micro-environment, and that it will assure that, is a real challenge. Do we really understand the micro-environment across the entire bioreactor, as opposed to where we sample? Are there scale-dependent process parameters that you really can’t make a scale-up without changing? Finally, the models you might use to do this – that is an area in small molecules people are thinking about. I think it is harder to model some biological manufacturing steps, but it is something people really want to think about.

OBP Pilot Program

The other implementation issue I want to talk about is our pilot program which started in 2008. The purpose of this is to define clinically relevant attributes for protein products and link them to the manufacturing process.
In doing this we would consider QbD approaches to unit operations in supplements – and we are aiming for ten, as well as five original applications, and to explore the use of protocols. Although we have had protocols for a long time in the US, we haven’t necessarily used them to the fullest extent. We are, similar to Europe, learning a lot about how these protocols could be used. Because we had a very robust filling of the original five applications, but less interest in the supplements, we have increased the number of original applications to eight and we have extended the period to apply for another year.

So, where are we? We’ve got some applications accepted – five original applications, four monoclonal antibodies and one Fc-fusion protein, which is related to antibodies, so we have a real bias towards antibodies. We are interested in exploring other therapeutic proteins, because I think the knowledge we gain from them is different. We had four post-approval supplements, two monoclonal antibodies, one therapeutic protein, and one that covers multiple products, which I think is an important area.

What knowledge can be moved across different products? One is site transfers, and we are working closely with Compliance on that. We have developed, at least for the biological side, an agreement about separate roles and responsibilities with Compliance…it is extremely important to figure out how to work with the GMP side in terms of doing this well.

We have had some meetings already, no submissions. We have had seven meetings so far, and a couple more planned. So what can we learn from this? I have to say this is like getting water out of a rock, because from seven meetings you will not garner that much information.

We had a total of 29 questions that industry asked us…. 25 of them related only to antibodies, but four included other therapeutic proteins. The general categories we got asked questions on: 13 were design space, six on risk assessment methods, four on control strategy, four on expanded change protocols, and three on the adequacy of small scale models. The meetings all went basically the same way. The company presents us their approach, they ask if the agency agrees. The agency says, ‘yes, we agree in principle, but until we see the actual data we can’t answer.’ So it isn’t very hard to predict the interactions.
RX-360 is an international consortium of pharmaceutical and biotech companies and suppliers to the industry, incorporated in 2009, that aims to develop and implement a global quality system to help members ensure product quality and authenticity throughout their supply chain to enhance patient safety.

VALUE PROPOSITION

The consortium will create a win-win approach for all interested parties.

Patients will benefit due to the enhanced security of the supply chain and improved product quality.

Regulatory bodies will benefit from the improved security and quality, which will allow them to focus their limited resources on other areas that create public health risks.

Pharmaceutical and biotech product manufacturers will benefit by protecting and improving the quality of raw materials, components, excipients and active pharmaceutical ingredients; by reducing rejects, investigations and audit burden; by improving cycle times; and by allowing internal resources to be redeployed to other quality efforts, such as working with their suppliers.

Suppliers will benefit from clear and consistent auditing standards, the reduced number of individual customer audits and the reduced administrative burden of audits.

Third party auditor firms will benefit from a more standardized audit approach, high-quality training, and a potentially increased customer base.

Professional and trade organizations will benefit from the opportunity to contribute and from access to comprehensive standards and training materials that they can use to benefit their members.

NEED FOR INDUSTRY ACTION

As regulators, pharmaceutical executives, supplier executives and members of professional organizations, our ultimate mission is to serve patients.

In order to achieve this mission, we require secure and reliable supply chains that deliver quality materials so that medicines can be trusted by health care practitioners and patients.

Legislators, regulators, and other organizations around the world are developing and implementing measures to curtail activities that undermine product quality or mitigate their impact.

Rx-360, as a global consortium, will complement these efforts and offer a level of consistency and scope world-wide that local measures cannot achieve.

1500 K Street, N.W.
Washington, D.C. 20005
Telephone: +1(202) 230-5608
Facsimile: +1 (202)842 8465
Email: kim.rouse@dbr.com
At a QbD/PAT regulatory workshop preceding the IFPAC 2010 conference in early February, European Medicines Agency (EMA) Scientific Administrator Evdokia Korakianiti offered a European regulatory perspective on the implementation of QbD. Korakianiti discussed the current status of QbD submissions and inspections in Europe, issues commonly raised during review of QbD applications, pre-approval inspections, implementation activities, post-approval changes, the role of assessors and inspectors, and activities of the European PAT Team.

This vision regarding pharmaceuticals was articulated by the ICH at a meeting in Brussels in 2002. The vision was to develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product that would emphasize an integrated approach to quality risk management and science. The guidelines that create the framework to enable such a vision are ICH Q8, Q9, Q10, and the draft Q11.

The main emphasis about quality by design – quality should not be tested into a product, but it should be designed in. Testing quality after the fact is too late, too costly and inefficient, as was already stated by Deming a long time ago. The development of this concept is no longer isolated. It lives across the lifecycle of the product, so we have a flow of information and knowledge. The new paradigm of quality is based on science, risk management tools, and the establishment of an efficient quality system. The integration of all these three elements would enhance the process for ensuring quality and would facilitate continual improvement.

What are we doing in Europe to facilitate the ICH vision? First of all we are trying to identify the knowledge gaps. And how do we do that? Through interactions with industry, the evaluation of the first applications we are receiving, and contacts that the European PAT Team has with industry. Once we identify the knowledge gaps, we are trying to build knowledge through workshops with industry, and expert meetings with industry and academia. Once we have gotten that knowledge, we need to share it with our network, so how do we do that? By developing questions and answers, and the guidance documents, and with training for assessors and inspectors. Of course, this is a never ending cycle. Every time we think we have solved something then new questions arise. So this is an evolution.

The measurement of quality is a never ending tale, but we want to move from quality by testing, which is the current paradigm, to quality by design.

Current Status of QbD Submissions and Inspections in Europe

So far we have received some submissions that have elements of quality by design in the applications. It started slowly with small numbers, but the numbers are gradually increasing. It seems that the companies that have received the first approvals then come again and again, quickly implementing these QbD processes across several products.

The submissions received so far for initial applications are about 16, post-authorization procedures are four, and scientific advice requests, two. Actually those applications that have a design space covered with a thorough control strategy, more or less are four. So we would ask how many true QbD applications have we received? There are not 16, there are much less. This is not surprising, of course. It is normal that industry would come and test the waters and see what is the regulator reaction. It is a learning process both for industry and for us. The vast majority of these submissions come from big pharma, and they are mainly for chemical active substances.

So, what is the picture for the future? What we see now is that this is starting for biological products as well, but we don’t see so many because the complexity of those products is higher. We have had some initial discussions with smaller companies showing there is a lot of interest in this respect, and they are trying to find their way towards that direction to implement QbD. It seems that it might take a bit more time compared to big pharma.

Issues Commonly Raised During Review of QbD Applications

One of the main problems when we see the submission is how the information generated during the development is reflected in the dossier. It seems there is a handicap there.
For example, in the case of **risk assessment**, quite often there is no information or minimal information of how the coding of the variables in an FMEA is happening. So what we might receive is a scored table with no interpretation of how this scoring has been developed, and of course this would raise a question. Even if an FMEA does explain or justify, there is no justification sometimes for the selection of the variables for further study. Quite often we see a table with some scoring, and it says we will continue to study variables that score higher than, let’s say, 16, without any explanation why. Of course this would raise a question.

Quite often, again, they discuss conclusions that are presented as a summary, with no explanation of how they have been reached. The assessor doesn’t know what they have been doing, and the dossier is the only way that they can present what they have been doing. They may have done fantastic work, but unless this is explained and they can take the assessors through it in the dossier, they will have questions.

With regards to **design space**: Quite often, again, the same problem. Sometimes there is minimal information about how critical parameters have been established.

A problem that is troubling regulators at the moment is that the design space in most cases is developed at lab scale and pilot scale. How do we verify the validity of the design space at production scale? Of course we would not expect that you perform the whole process at production scale. But on the other hand, how do you give assurance that those conclusions are valid above pilot scale and during the life cycle of the product? This information is missing in dossiers, and of course, raises questions.

In development of the design space, quite often the information about interaction between the factors under study is not there. This raises questions. Have they been looked into? Or have they been forgotten? This should be mentioned. Results of design of experiments (DOE) are either not shown, and they say ‘we have done this DOE and these parameters were found significant.’ So information is given and an assessor has to assess them with no data given to allow critical assessment. This causes problems.

Another issue is the boundaries of the design space are quite often not clearly described, so it is not very clear which, from all the parameters we have started with, will constitute part of the design space. Is it only the critical ones? Will it be some key ones? It is not clear in the end. It would be very useful if somewhere in the dossier the design space with the parameters and their ranges was clearly described in a table so someone can see the final design space, and the rest is development information. Sometimes ranges investigated at lab scale do not correspond to the design space applied for at production scale, and there is no explanation. Has it been scaled up? So there is a missing link there.

Another question that sometimes is raised is the clinical relevance of the design space. The variability the design space allows in the process – how does this affect the clinical performance of the product? We should not forget that quality is not assessed on its own. It is also in relation to safety and efficacy.

Another great area of questions and issues is **NIR**. NIR has been used as an at-line method up to now. There is a lack of experience in submissions for the use of NIR for on-line or at-line testing, like for process monitoring. Quite often companies struggle, and also assessors struggle, with the information presented in these cases. What should be in the dossier, and what should be outside? In these cases, changes are part of the necessary update of the model, and therefore should be subject to GMP, in which cases it tends to constitute a variation. The borderline is not very clearly defined.

When we develop a chemometric model, quite often there is not a lot of information about the composition of the data set for the creation of the model, for cross-validation and independent validation. We are not asking for a full scale evaluation, but some information about the goodness of fit and goodness of prediction should be there. I am sure that you have it in some of your notebooks. It should also be in the dossier. It doesn’t necessarily mean that if they ask for it in the changes it is going to be a variation, but we need to know how good your model is at predicting the data. How do we ensure that this model will remain valid throughout the product lifecycle? So what are you going to do? It is good to have the quality system of the company – but on the other hand, what is your strategy? Have you developed a method and then you will leave it like that forever? Not really. I am sure you won’t.
Similar questions for the methods used for multivariate data analysis [MVDA] and multivariate statistical process control [MSPC]. If you ask me now what sort of data should be in the dossier and what should be outside, I wouldn’t have a good answer, so please do not ask me. We regulators do not have all the answers, but we learn from experience and we [can tell when it is enough]. You know yourselves what information should be presented to make an assessor comfortable with the work you have done.

Another big problem that was specific for Europe at that time was how to deal with the possibility of regulatory flexibility that was mentioned and foreseen when ICH created QbD applications. In the past I remember at least three or four cases when we had to reject proposals for post-approval flexibility, not because they were not good, but because we didn’t have the framework that would allow flexibility for these types of products. At that time the variations regulation did not foresee downgrading different groups of changes based on the information in the dossier, based on the understanding of the product and the process.

[Also important] is terminology. In each dossier we find a different set of terms. Why don’t we develop a common vocabulary? It causes quite a lot of confusion to the assessors. This is not a major issue, but why do we need to cause this additional complexity?

Pre-approval Inspections

One of the questions that we see is companies asking ‘are we going to have a pre-approval inspection?’ It is not a rule. At least in Europe when we had proposals for real-time-release testing, there was a pre-approval inspection requested. Up to now we have had three pre-approval inspections with applications, and one was joint with FDA. What did we request? The inspector looked at how the design space was integrated, translated into the batch records, and also looked at the batch release procedures, and the GMP of the quality system.

The inspector needs to have a very good understanding of the ICH Q8, Q9, and Q10 concepts. They need to have a very good understanding of the dossier and the application. They need to have some sort of understanding about the analytical techniques and methods used in the analysis, the risk assessments involved, and MVDA. They don’t need to be experts, but they need to have an understanding of that, otherwise they cannot communicate with the company. This means there is a need for a very close collaboration and interaction between assessors and inspectors.

What we found very interesting is the borderline between assessment and inspection. Sometimes an inspector thinks this is subject to GMP inspection, and they will go into some detail. On the other hand, we cannot expect any inspector within this limited amount of time to evaluate MVDA models during an inspection. This is not feasible. They cannot review raw data, and that is not the point. [Raw data will only be reviewed] if the assessor is concerned about the validity of something. The inspector will mainly focus on system-related issues – for example, how the design space is implemented in batch records, how excursions from the design space are handled, the MVDA model lifecycle, validation, etc.

Activities to Facilitate Implementation in Europe

After we have made a summary of assessment issues and inspection observations, what are we doing in Europe to facilitate implementation? First of all we looked at some of the existing guidelines and started to revise the relevant ones. We tried to create a framework that would enable post-approval regulatory flexibility. We have identified some areas for additional guidance, and we have activities to facilitate the transfer of knowledge from the PAT team to the whole network of assessors and inspectors. Europe is a very complex network consisting of 27 member states, different national authorities, so it is a big challenge to infuse all this knowledge to all the assessors and inspectors.

In the existing guidelines: The current guideline on the use of NIR is under revision. It has been put out for consultation, and received quite a lot of comments from industry. Another guideline that has been identified for revision is the one for parametric release. The parametric release guideline as it stands right now is focused on sterility testing. However, we believe in a QbD environment that we will have real-time release testing and other tests apart from sterility testing [draft now released – see p. 20].
Post-Approval Change Management Protocols

Post-approval regulatory flexibility was not possible until the end of 2009. We are quite happy to say that now this has been taken care of, and the revised variation classification guideline introduces the concept of post-approval change management protocols. The US has quite some experience with them – they are the so-called ‘comparability protocols.’ Such a protocol will describe the specific changes that the company would like to implement during the lifecycle of the product, and how these would be prepared and verified. We see these protocols as a means to facilitate post-approval regulatory flexibility. They are applicable to all types of products, both chemical and biological, and to all applications, both traditional and quality by design. However, we believe that quality by design applications will realize the full potential of such protocols.

So, up to now, if a change was to be implemented, we would receive the full packet as one whole. That would be evaluated as one whole – that would be the strategy, studies, acceptance criteria, and the methods, plus the results. Now, the strategy will be assessed in an earlier step, which will be the submission of the protocol, and the results will follow up in a second step, and will be implemented with a quick implementation step where we will allow a downgrading of the change. For traditional applications this might be beneficial in the sense that it will be more predictable for companies about how to implement the changes. In a QbD setting, it is a more risk-based approach. Instead of giving the full set of data, just dividing the assessment in two steps, you would expect a more risk-based approach in the evaluation.

It is a new concept for Europe, and there has been a lot of brainstorming with regards to what types of changes could be allowed in these protocols. Would we request a protocol for changes? Would we allow, for instance, for a QbD application, one protocol affecting all CPPs in the same process? And how would this be handled? How would this work? The Quality Working Party seems to be taking a wide approach, but these have only been recent discussions. What type of studies do we need to have? The amount of data in the protocol – will the protocol have no data at all or will we be requesting some pilot data to support the protocol? How do we ensure that this protocol is going to be feasible? How do we avoid the risk that the protocol is submitted, and then at the second step, the company shows that well, it was not realistic, so it cannot be applied?

Role of Assessors and Inspectors

At the moment in the Quality Working Party and the Biologicals Working Party there is a lot of work ongoing.

With respect to the role of the assessor and inspector, it doesn’t change, in the agency. As an agency, we need to bring down the silos. We need to increase collaboration and communication. It is very important to improve the flow of information between them. One of the actions we are taking is to revise the assessment reports. We have given more guidance, and we have created a kind of summary document at the end that could be transmitted to the inspectors. They can have a quick, very good understanding of the application – what is the design space, what is the flexibility applied for – so that we help them when they go for an inspection. Usually when it is a pre-approval inspection they are accompanied by an assessor.

We need to develop knowledge and guidance. First of all, the level of information that goes into the dossier: information about development of the design space, and the scaling up of the design space – level of information with regards to risk assessment. What are the requirements for real-time release? Can we rely only on pilot-scale data and say yes, they are very robust, we are happy, you can go ahead with real-time release? Do we ask for some pilot testing or for additional end-product testing together with real-time release? If yes, how many batches, for how long?

Another point, how do we deal with models? Management and maintenance for multivariate data analysis models, analytical development, and the lifecycle verification?
A point that causes a lot of discussion is the acceptance criteria for large sample sizes, especially with regards to content uniformity testing. There is ongoing work from EDQM. QbD for analytical methods – another topic that we need further work on. New manufacturing methods, like continuous processing – how do you do validation? How do you do sampling in this context? What are we doing in Europe to increase the knowledge of the assessors and inspectors with regards to these concepts? We have developed training and guidance documents. First of all, we have the ICH Working Group’s questions and answers document that provides some clarification on topics that have been moved forward. There are ongoing activities within the Quality and Biological Working Parties. At least with the Quality Working Party, over the last one and a half years, presentations have been given in each working party on different aspects of QbD application to increase awareness of the assessors.

In order to enhance collaboration between assessors and inspectors, we have joint meetings of the Quality Working Party with the Inspectors Working Group to ensure they are understanding and are in agreement about how we deal with certain concepts. We have done training for assessors, and training is never enough. We have had two trainings for assessors specializing on quality by design….

A new guidance for how to draft assessment reports for QbD applications is about to be published. We also have peer review. Assessors are not alone when they do these applications. We have the PAT team that will do the preview of these applications to be sure they are aligned with the concepts that have been discussed.

There are also interactions with industry. Just some examples: I mentioned the workshops that we had with EFPIA on design space and quality-by-design applications back in 2006 and 2009. We have had some mock inspections organized with EFPIA and reviewed some submissions in the context of the EU PAT Team.

**Activities of the European PAT Team**

Last but not least, I would like to highlight the activities of the European PAT team. It acts like a gateway at the moment for quality-by-design applications, through the centralized procedure. So it is a team. Its role is to prepare a harmonized approach within Europe for the assessment and inspection of applications. And the vision is – I cannot say for how many years, but sooner or later – that this becomes common practice and we won’t need the PAT team. This is going to be the status of the manufacturing and the design of medicinal products in Europe.

The activities of the PAT team were first of all to try to find answers to knowledge gaps that exist. Moreover it will be implementation and training of assessors to familiarize them with the new concepts, to develop guidance, and to ensure at some point that this will become common practice.

So, what is this team doing? It gives advice to industry, high level on strategy issues. It publishes Q&A documents and organizes training for assessors and inspectors. It gives input to scientific advice for quality by design applications. Some of the Quality Working Party who are members of the team participate in ICH activities.

As a conclusion, the concepts are still relatively new in the field of pharmaceuticals, and issues keep arising as experience is gathered. The assessors are at this point being requested to evaluate new types of data, and there is a need for appropriate expertise. And we are trying to address that by developing additional guidance and by organizing training. Europe is actively participating in the ICH Implementation Working Group activities to ensure we have a harmonized approach in the implementation of these concepts. We wouldn’t like to have the regions implementing these concepts in a different way. It just would not make sense.
Willing to take a Guess?

CMC Biologics can take the guess work out of your process development and biomanufacturing. We have solutions for the challenges you will face on the way to market approval. Overcome your first challenge by choosing a manufacturer that values transparency in working with you.

A unique proposition:
- Mammalian and microbial platforms
- Solutions from DNA to commercial supply
- Biomanufacturing in both US and Europe
- Extensive Protein Characterization and Formulation capabilities

With facilities in Copenhagen and Seattle, and production scales ranging from 100L to 3000L, we have the infrastructure to meet your needs.

But it’s our people, their know-how and our passion for delivering high quality biotherapeutics, that makes us a top-tier solutions provider.

www.cmcbio.com
Take a Closer Look

Meet us at our exhibition booths at the following upcoming international conferences:

<table>
<thead>
<tr>
<th>Conference</th>
<th>Date</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioProcess International Conference &amp; Exhibition</td>
<td>20 – 24 September 2010</td>
<td>Providence, Rhode Island, USA</td>
</tr>
<tr>
<td>CPhI Worldwide 2010</td>
<td>5 - 7 October 2010</td>
<td>Paris, France</td>
</tr>
<tr>
<td>Bio-Europe 2010</td>
<td>15 - 17 November 2010</td>
<td>Munich, Germany</td>
</tr>
</tbody>
</table>

If you would like to schedule a meeting at one of these events, contact one of our Business Development team via our website: [www.cmcbio.com](http://www.cmcbio.com)

Or just drop by our booth.

We look forward to meeting you in Providence, Paris or Munich!

www.cmcbio.com
At a Product Quality Research Institute (PQRI) conference on “advancing drug product quality and development” in December, CDER Office of Pharmaceutical Science Research Policy Associate Director Nakissa Sadrieh addressed emerging regulatory considerations for nanotechnology-containing therapeutics. Sadrieh discussed how nanotechnology is defined, why nanoparticles are being used, FDA’s action on nanotechnology, quality assessment and safety considerations for CDER products, and concerns and initiatives in developing a regulatory framework. The role that PQRI can play in helping advance the scientific foundation for nanotechnology regulation was one of the focal points of the conference. Sadrieh is chair of CDER’s Nanotechnology Working Group and has been actively involved in PQRI activities.

There is a lot of hype and excitement and promise associated with nanotechnology, and so the FDA is looking at issues regarding this area. I am going to give you a little presentation on some of the regulatory considerations that are linked to nanotechnology-containing products…. The impact of nanotechnology is likely to be on many of the products the FDA regulates such as cosmetics, food and devices. I will be focusing more on therapeutics.

What Is Nanotechnology?

So when we talk about nanotechnology, what sort of size range we are talking about? I guess if you look at the tennis ball through the water molecule, the area that we are focusing on is around things such as glucose or antibodies, viruses – anything under bacteria and here it is around 1,000 nanometers.

The way nanotechnology is being defined right now [by] organizations [such as] the National Nanotechnology Initiative, which is a governmental multi-agency organization that has had a big part in initiating some of the research and definition in this area…is research and technology development at the atomic, molecular or macromolecular levels at the scale of approximately 1-100 nanometers. And actually, if you look at most of the definitions that are around, the focus is really on this 1-100 nanometers. However, this is something that is an issue that we at the FDA are looking at because it is not so simple, and we don’t think that the size limitation at the 100 nanometers is going to be actually something that is feasible for a drug product, and we will get to that in a minute.
So, basically, multiple definitions are really available for nanotechnology, but most of them, as I said, focus around the size limitation of around 100. But there are some limitations which go much higher. The European Science Foundation, for example, puts the size somewhere around several hundreds of nanometers without really defining what hundreds are. This is something that I think we feel more comfortable with. What's nano? Nano is under a micron. So pretty much 999 nanometers is nanotechnology, we think.

This is one of the reasons the FDA really does not have an official definition. The definition is going to be useful if you are going to have some sort of policy or some sort of regulations associated with it. So, if we say, 'ok, if you fall in this size range, this is what is going to happen to you,' we don't have the 'this is going to happen to you' part. So right now we really don't have a definition for nanotechnology. This is not to say that we do not regulate products that are in the nanoscale range. It is just that we do not define them in any particular way. We regulate them just as if they were other products.

If we look at the success of nanotechnology over the past three years, you can see that we looked at just three kinds of nanoparticles: liposomes, dendrimers and nanoparticles, which could be things such as nanocrystals or other kinds of nanoparticles. We can see that the number of publications has been increasing really quite exponentially in this field. Liposomes, I guess, have more publications, just because we started to get approval of certain liposomes in the early nineties. More recently we started getting certain products such as nanoparticles approved, and also some dendrimeric products that are being developed. So, the number of publications in those areas has also gone up.

But, with respect to drugs, what are we calling nanotechnology? Well, since we don’t have a real definition, we started looking at what is being called nanotechnology in the literature, and we notice that there are several types of structures such as liposomes, micelles, dendrimers, metal colloids, nanoemulsions, quantum dots, and then fullerenes and carbon nanotubes.

These are the types of things that we have identified right now that have some sort of link to possible therapeutic development and that we may be seeing at the FDA whether we have seen them already – things such as liposomes and micelles and there are some dendrimers in development. But in the future, other kinds [such as] quantum dots and fullerenes are possibilities. So, I think that when we talk about drugs, this list while not comprehensive is pretty close to being the universe of nanotechnology with respect to drugs right now, and I would say maybe in the next couple of years.

But, if we look at the future, I think that nanotechnology is going to take other shapes as well. The thing that is the most common between all these things, I think, is the fact that they are drug delivery systems. A lot of these nanoparticles have this capacity to target things and to deliver a payload basically to a particular site. There are things such as polymeric and biodegradable nanoparticles, ceramic inorganic nanoparticles, polymeric micelles, liposomes as I talked about. There are possibilities for sort of mixing and matching some of these types of nanoparticles for the future.

**Why Nanoparticles?**

So why are people looking at trying to make nanoparticles? There are some advantages, and one of them is, as I mentioned, the fact that you can target drugs. Either you can do it passively – for example, by taking advantage of things such as the leaky vasculature in tumors you can cause drugs to actually accumulate to a site – or by active targeting by actually putting some receptor ligands on a multi-functional structure and targeting the drug.

There are things that you can do also to improve the PK profile. When you decrease the particle size, you tend to increase the surface area, and so there are possibilities of having much better bioavailability. This is something that several companies have taken advantage of – reformulated their drugs to actually improve the bioavailability of their product by decreasing the particle size. And so, you
can improve the PK and also increase the drug concentration at the site of action, and by doing this maybe you can decrease the amount of systemic exposure to sites where you would not be getting any benefit. The goal would be to lower the toxicity.

Some of these structures also can serve as scaffolding. You can make multi-functional molecules, constructs, and then to these scaffolds you can attach various kinds of moieties. And so you can have something that has got a targeting as well as a therapeutic as well as an imaging agent attached to it, and so you can do lots of things with it. And you can alter the surface of these things by actually putting moieties on them to increase their solubility or decrease their clearance. In this drug delivery, some of the other advantages could be cost benefit. You can extend the lifespan of a product by reformulating it — certain people have taken advantage of that already — and you can enhance the effective patent protection.

You start actually bringing personalized medicine into the realm of reality because you can then make these constructs that are very specific, and then you put targeting moieties on them that are very specific to the actual tumor that you are trying to treat in the patient. And so you can tailor the treatment such that you can get optimized risk-benefit ratio.

FDA Action On Nanotechnology

I have given you a very short introduction of the world of nanotechnology with respect to its impact on drugs. What then has the FDA done to deal with this new area (whether it is new or not is debatable)?

In 2007 there was a Nanotechnology Task Force that was created by the then commissioner. The purpose of it was: • to actually enable development of safe and effective products • to address the knowledge or policy gaps that may be out there right now • to guide the science and technology • to assess the current state of the science, and • to strengthen collaboration with federal agencies.

The task force took a year to look at the issues and then issued a report. The report is really the starting document from which we have been operating basically at the FDA and the other activities that we have gotten into, which I will talk about in a few minutes, have really started from.

What did this task force really end up reporting? It concluded that there were two scientific issues and four regulatory policy issues. The two scientific issues were: 1) understanding the interaction of nanoscale materials with biological systems, and 2) assessing the adequacy of the testing approaches that we currently have. The four regulatory policy issues were: to look at the ability of the FDA

NANOPARTICLE DEFINITIONS

- **Liposomes**: vesicles composed of one or more bilayers of amphiphatic lipid molecules enclosing one or more aqueous compartments.
- **Micelles**: self-assembling nanosized colloidal particles with a hydrophobic core and hydrophilic shell currently used for the solubilization of various poorly soluble pharmaceuticals.
- **Dendrimers**: polymers in which the atoms are arranged in many branches and sub-branches along a central backbone of carbon atoms.
- **Metal colloids**: a state of subdivision, that the molecules or polymer particles dispersed in a medium have at least in one direction a dimension between 1 nm and 1 micron, i.e. silver, gold, and iron oxide.
- **Nanoemulsions**: emulsions with droplet size in the nanometer scale. Emulsion is a thermodynamically unstable system consisting of at least two immiscible liquid phases, one of which is dispersed as globules, in the other liquid phase, stabilized by the presence of an emulsifying agent.
- **Quantum dots**: nanoparticles that exhibit size-dependent electronic and optical properties due to quantum confinement.
- **Fullerines**: closed cage structures having more than 20 carbon atoms consisting of three-coordinate atoms.
- **Carbon nanotubes**: seamless tubes constructed from graphene that can be either a single-wall or multi-wall nanotube comprising concentric tubes.
to identify FDA-regulated products that contain nanoscale materials – while this may seem obvious, it actually is not; looking at the scope of the FDA’s authority regarding evaluation of safety and effectiveness; the third one was labeling; and the fourth one was the NEPA, which is the National Environmental Policy Act.

• If we go to the first science recommendation, which is to understand biological interactions, the recommendations were that clearly more knowledge was needed about biological interactions, and detection and measurement capabilities. The science isn’t really clear in that area, so these are some of the things that are not allowing us to actually make specific policies. And again, in-house expertise and infrastructure needed to be built up – so that is a weakness on our side that we need to work toward trying to fix. And agency-wide regulatory-science coordination was needed in this area.

• The science recommendation number two involved whether our testing approaches are currently adequate or not. The current testing approaches to assess safety, effectiveness, and quality of products with nanoscale materials should be evaluated. While I think the policy right now is that our methods are adequate, we have to keep looking at them and determine whether they are actually going to be adequate for a long period of time, and so their evaluation is needed. And we need to promote and participate in development of characterization methods and standards for nanoscale materials as well as development of models for the behavior of nanoscale particles both in-vitro and in-vivo.

• Regulatory policy issue number one, identification of products containing nanomaterials: The recommendations were to issue guidance so that sponsors could actually identify particle size and so make that known to us, and when warranted, we should issue a call for data on particle size for over-the-counter drugs, foods and color additives.

• Regulatory policy number two, looking at the scope of the FDA’s authority on product safety and effectiveness: A Federal Register notice should go out to call for safety and effectiveness data on these products so we can evaluate those and determine how we need to proceed. Again, guidance needs to be put out on products that are both subject to premarket approval and those that are not subject to premarket approval. We actually had a couple of public meetings already and the result of these recommendations is in the task force report, and there is a guidance document that is currently being drafted at the commissioner’s office to try and deal with the issue of identifying these products. It is not out, yet, but it is going to be coming out soon. So some steps have been taken by the agency to try and address these recommendations.

• The third and the fourth recommendations are very similar: The recommendation is that the labeling has to be addressed on a product-by-product basis – whether you actually need to provide information on whether something contains nanoparticles or not in the label; and that for NEPA, you have to consider it again on a product-by-product basis whether the FDA-regulated product actually qualifies for an existing categorical exclusion or whether extraordinary circumstances exist.

So, this is just an overview of what the task force recommendations were and what the report was about.

Nanotechnology In CDER Products

Now I will talk about some of the products and nanotechnology in CDER, the marketed products and future applications.

Some of the current marketed products that contain nanoparticles right now are things such as sunscreens that contain nanoscale titanium dioxide and zinc oxide. There are some reformulations of previously approved products, such as nanoemulsions, nanocrystal colloid dispersions, liposomes and iron oxides.

I put together a list – it is not a comprehensive list – of approved products on the market. If we look at things such as liposomal platforms, we can see that there are a number of them already approved. And we can see that the size range is not limited to under 100 nanometers, clearly. But liposomes are called nanotechnology, so we just included them in here. Things such as nanocrystal colloid dispersions. These are some reformulations of previously existing products, and these are a little bit smaller than some of the liposomes.
And there are other platforms. There is an iron oxide, a nanoemulsion, and Abraxane which is an albumin-coated nanoparticle. This is just to give you the idea that we do have products on the market that are in a nanoscale. Some of them larger than nano, but they are called nanotechnology.

What are some of the considerations for regulating these things? Really they fall into two areas: one is product quality assessment and the other one is safety assessment. Quality assessment is how do we characterize them, how do we do quality control and how do we manufacture these things. In the safety assessment, the real importance there is biodistribution, clearance, metabolism and toxicology.

Quality Assessment

If we look at the characterization needs: I am going to be listing a number of gaps out there that we feel need to somehow be addressed by research or by data, so they can help us regulate these products the best way that we can.

There needs to be the development of appropriate tools and methodologies to adequately assess the product chemistry and its unique characteristics. What is important to keep in mind is that we are not just looking at the bulk product. We have to look at the complete formulation, because with these nanoparticles the likelihood that their properties actually change when you put them into a complete formulation is very big. So you really cannot just look at whether something contains a nanoparticle before formulating it. You have to look at it.

This has been an issue with sunscreens, for example. While people say, ‘well we started out with nanoparticles, but then by the time they were formulated, it has aggregated and agglomerated.’ That is true, but the bottom line is there is going to be a range of structures there, and the formulation is going to impact that, so that needs to be determined.

We also need to enhance the quality control measures so we can make consistent products batch-to-batch. And we have to have a way of being able to link the product quality to performance. We need to know the critical quality attributes, so that if there are some changes in those types of attributes we would be able to determine how they may impact the quality of the product as well as possibly safety.

If you look at some of the properties of nanoparticles, you can make quite a long list depending on the type of nanoparticle that you are looking at. There are things associated with the morphology of the particle, the surface properties, its chemical computation, and there could be other types of properties. If you break these down for the type of nanoparticle that you are looking at, you can have a number of different properties to look at. And each property you could look at using a number of different techniques, and you can look at some parameters in a number of different ways.

I think that what I am trying to bring across is really two things: What, I guess, we don’t know right now is, for the type of nanoparticle that we may be looking at, what are going to be the important properties that we need to know? So for a dendrimer or a carbon nanotube, what is the important property that we need to know? What is the best way for us to be able evaluate those properties? If somebody could actually generate a table with the particle, the property and the methods that one would use to actually evaluate or characterize, that would be a great help to be able to adequately review these products and to know whether there are issues that we need to look at or not.

And the other point that I wanted to make is that if you look at these properties, some of them are quite different from the normal properties that we look at right now for small molecules [e.g.] electron microscopy methods [see box on following page]. These are not methods that have been used in the past in manufacturing. So we need to find ways of being able to identify methods that are going to be adaptable to be able to actually develop drugs. This may be one of the reasons that large pharmaceutical companies have not really gotten into developing these types of structures. Many of these have been from smaller companies up to now.
APPENDIX IV

PROPERTIES/TECHNIQUES FOR NANOPARTICLE ANALYSIS

<table>
<thead>
<tr>
<th>Propertiesa</th>
<th>Common Techniquesb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphology</strong></td>
<td></td>
</tr>
<tr>
<td>Size (primary particle)</td>
<td>TEM, SEM, AFM, XRD</td>
</tr>
<tr>
<td>Size (primary/aggregate/agglomerate)c</td>
<td>TEM, SEM, AFM, DLS, FFF, AUC, CHDF, XDC, HPLC, DMA(1)</td>
</tr>
<tr>
<td>Size distribution</td>
<td>TEM, SEM, AFM, DLS, AUC, FFF, HPLC, SMA</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>SLS, AUC, GPC</td>
</tr>
<tr>
<td>Structure/shape</td>
<td>TEM, SEM, AFM, NMR</td>
</tr>
<tr>
<td>Stability (3D structure)</td>
<td>DLS, AUC, FFF, SEM, TEM</td>
</tr>
<tr>
<td><strong>Surface</strong></td>
<td></td>
</tr>
<tr>
<td>Surface area</td>
<td>BET</td>
</tr>
<tr>
<td>Surface charge</td>
<td>SPM, GE, Titration methods</td>
</tr>
<tr>
<td>Zeta potential</td>
<td>LDE, ESA, PALS</td>
</tr>
<tr>
<td>Surface coating composition</td>
<td>SPM, XPS, MS, RS, FTIR, NMR</td>
</tr>
<tr>
<td>Surface coating coverage</td>
<td>AFM, AUC, TGA</td>
</tr>
<tr>
<td>Surface reactivity</td>
<td>Varies with nanomaterial</td>
</tr>
<tr>
<td>Surface-core interaction</td>
<td>SPM, RS, ITC, AUC, GE</td>
</tr>
<tr>
<td>Topology</td>
<td>SEM, SPM, MS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Propertiesa</th>
<th>Common Techniquesb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical</strong></td>
<td></td>
</tr>
<tr>
<td>Chemical composition (core, surface)</td>
<td>XPS, MS, AAS, IPC-MS, RS, FTIR, NMR</td>
</tr>
<tr>
<td>Purity</td>
<td>ICP-MS, AAS, AUC, HPLC, DSC</td>
</tr>
<tr>
<td>Stability (chemical)</td>
<td>MS, HPLC, RS, FTIR</td>
</tr>
<tr>
<td>Solubility (chemical)</td>
<td>Varies with nanomaterial</td>
</tr>
<tr>
<td>Structure (chemical)</td>
<td>NMR, XRD</td>
</tr>
<tr>
<td>Crystallinity</td>
<td>XRD, DSC</td>
</tr>
<tr>
<td>Catalytic activity</td>
<td>Varies with nanomaterial</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Drug loading</td>
<td>MS, HPLC, UV-Vis, varies with nanomaterial</td>
</tr>
<tr>
<td>Drug potency/functionality</td>
<td>Varies with nanomaterial</td>
</tr>
<tr>
<td>In vitro release (detection)</td>
<td>UV-Vis, MS, HPLC, varies with nanomaterial</td>
</tr>
<tr>
<td>Deformability</td>
<td>AFM, DMA(2)</td>
</tr>
</tbody>
</table>

a The property list is not definitive. Other properties may be reported.
b Only common techniques are listed. Other techniques may be valid. The choice of techniques should be justified.
c These techniques will measure the average particle size, but can not necessarily distinguish between primary particles, aggregates, and agglomerates.

TESTS FOR NANOPARTICLE ANALYSIS

| AAS | Atomic absorption spectroscopy |
| AFM | Atomic force microscopy |
| AUC | Analytical ultracentrifugation |
| BET | Brunauer, Emmett, and Teller method |
| CHDF | Capillary hydrodynamic fractionation |
| DLS | Dynamic light scattering |
| DMA (1) | Differential mobility analyzer |
| DMA (2) | Dynamic mechanical analyzer |
| DSC | Differential scanning calorimetry |
| ESA | Electroacoustic spectroscopy |
| FFF | Field flow fractionation |
| FTIR | Fourier transform infrared spectroscopy |
| GE | Gel electrophoresis |
| GPC | Gel permeation chromatography |
| HPLC | High performance liquid chromatography |
| ICP-MS | Inductively coupled plasma mass spectrometry |
| ITC | Isothermal titration calorimetry |
| LDE | Laser doppler electrophoresis |
| MS | Mass spectrometry (GCMS, TOFMS, SIMS, etc.) |
| NMR | Nuclear magnetic resonance |
| PALS | Phase analysis light scattering |
| RS | Raman spectroscopy |
| SEM | Scanning electron microscopy |
| SLS | Static light scattering |
| SMA | Scanning mobility particle sizer |
| SPM | Surface probe microscopy (AFM, STM, NSOM, etc.) |
| TEM | Transmission electron microscopy |
| TGA | Thermal gravimetric analysis |
| UV-Vis | Ultraviolet-visible spectrometry |
| XDC | X-ray disk centrifuge |
| XPS | X-ray photoelectron spectroscopy |
| XRD | X-ray diffraction |

MAY 2010 | 59
Safety Considerations

Focusing quickly on the safety considerations: I guess some of the concern up to now [has been] that nanoparticles are not safe because they are small and they do strange things. What we need to understand first is, what does safety mean? Safety is really the dose that doesn’t result in toxicity, so it doesn’t mean that it’s just absolutely safe. This means we are talking about relative safety, which has a risk/benefit ratio, and it is going to depend on many factors, including the disease and the target population. So clearly for something like cancer, you are going to be likely to take a lot more risks and you will accept certain types of toxicities that you may not accept for a drug that will be treating, for example, obesity or depression.

And then, how do we measure safety? It is measured in clinical trials as well as preclinically. Quickly to go over a preclinical safety assessment: What preclinical studies have done in the past traditionally was to answer the questions that one could not answer with clinical studies – questions such as: Can women of child-bearing age take the drug – might there be harm to the fetus? Or will prolonged exposure result in cancer? To guide the clinical studies, we do the preclinical studies, and this is going to depend on factors such as the formulation, the route of administration, as well as the clinical population. So the clinical safety assessment is really to evaluate things such as genotoxicity, carcinogenicity, histopathology and the developmental toxicity, as well as to help establish a starting dose in humans.

The safety considerations that are raised by nanomaterials are: • Do nanoparticles gain access to tissues and cells normally bypassed by larger particles? That seems to be something people are concerned about because they are small. They maybe go to places. • What effects do they have on cellular and tissue functions • Would those be transient or permanent? • How long do they remain at the site? • And how are they cleared from tissues and blood?

With respect to ADME [absorption, distribution, metabolism and excretion]: • Can nanoparticles be appropriately labeled for being able to do ADME studies? • Would you actually affect their properties by labeling them? • Is the biodistribution of a nanoparticle different than that of a larger sized particle? • Are there adequate methods for measuring nanoparticles in the blood and tissues? What is your limit of detection? Can you distinguish between the nanoparticle and the aggregates? And then what is the accuracy of the mass balance studies, and could the clearance of targeted nanoparticles be accurately assessed?

I just listed a bunch of questions that we have basically raised when we have talked about the things that are of concern to us. While these are not unique questions – we have asked them for lots of other types of products – they have come up for nanomaterials. If there are unique characteristics associated with nanoparticles and we cannot answer these questions, that is where we are going to have difficulties.

So the current preclinical tests for safety evaluation of drugs are things such as: pharmacology, where we look at mechanism of action; safety pharmacology, where we evaluate things such as the EKG; toxicology, where we actually do clinical pathology and histopathology; genotoxicity; developmental toxicity – which is reproductive toxicology; immunotoxicology; carcinogenicity; and other types of tests depending on the route of administration or the disease that one may be evaluating.

With respect to the adequacy of the current preclinical tests, we feel that the existing battery of preclinical tests is very rigorous, because high dose multiples are used. There are at least two animal species used. Extensive histopathology is done on most organs, and functional tests are looked at – the cardiac system, neurological system, respiratory, reproductive – and then animals are treated for extended periods of time. Carcinogenicity studies go up to two years, and so there is data on relatively long-term exposure.

What about additional tests, what would you do? Would do you something extra for nanomaterials? In general, we don’t just depend on the preclinical. There are clinical studies as well. Clinical studies are conducted in healthy volunteers, and patients and people with organ impairment or at-risk populations. We feel that with the combination of that, we should be able to address any of the questions that might be out there. But again, it is not to say that there will be one type of nanomaterial that is going to pose human challenges.
Are, then, additional screening tests needed? The answer to that would be only if there are things that our current tests miss and that there are endpoints that additional tests would measure. This is to answer one of the questions that was raised by the nanotechnology task force report…. So we went through this evaluation of our current testing approach. For right now, we feel that we are probably in good shape and that we do not need additional tests for regulating nanomaterials. And this is only for drugs, again, as I said. It may not apply for things such as cosmetics.

Developing A Regulatory Framework

What are important considerations towards the development of a regulatory framework for nanotechnology-containing drugs? Some of the considerations are:

• Can we identify products containing nanomaterials in already submitted applications? This is not actually obvious. The answer probably to this is mostly no. Right now we are going through an exercise of trying to develop an in-house database of products that we have at the FDA – ones that we have approved, and another list of products that we have to determine whether there are nanoscale materials in those products so that we can link any kind of adverse event or any kind of toxicity or something to the particle size. It is not so easy identifying whether there are nanoparticles in them or not, because if the particle size is not relevant or not deemed relevant, nobody is going to actually report the particle size. That has been one of the concerns – we actually don’t have ways of identifying things that contain nanomaterials. So we are taking steps towards dealing with that.

• Can we identify nanomaterial-containing products in future applications? Kind of similar to what I just said.

• How do we define nanotechnology for the purposes of drug review and evaluation? Again, I did mention that we don’t have a definition, but a definition is something that people do like. I think once we have figured out how we are going to evaluate these products, that is when we would need to have a definition, so they either fall under that definition or not.

• And is there a need to develop specific policies to address nanomaterial-containing products? For right now the answer is no, but in the future that is something that may be necessary.

With respect to guidance, most of the already existing guidances out there are going to apply to nanomaterial-containing products. There is no need for specific guidance, but there is an agency-wide guidance that is being developed right now that I mentioned at the beginning to cover the use of nanoscale materials in FDA-regulated products. The bottom line for that guidance is that sponsors need to tell the FDA that your product contains nanomaterials. It is recommended that they contact us to let us know that. Also, some centers are considering developing either MaPPs or guidance documents. I think that our center, CDER, is working on a MaPP. We have finished drafting it. It is going through the channels. But it is a MaPP that is going to help with identifying whether the applications contain nanomaterials or not. So CMC reviews will have to track certain types of information in the application to make us better be able to track these things.

The CDER initiatives that are in progress: the development of the database that I mentioned; the development of procedures and SOPs – basically, the MaPPs. We are also doing some research and the research projects involve understanding the properties of nanoparticles in CDER-regulated products that require adequate characterization. We will try to understand the instrumentation that does best to characterize nanoparticles in CDER-regulated products. We are trying to evaluate whether you get dermal penetration of things such as titanium dioxide in sunscreens. We have actually completed this study and the answer is no. And we are using the nanotechnology database under construction to identify additional gaps that may require a policy.
At a quality systems interest group session at PDA’s 2009 annual meeting, Genentech Director of Corporate Quality Christa Hartmann highlighted knowledge management as a central problem for companies in their efforts to advance the new Q8-10 paradigm. Without offering ready-made solutions, Hartmann laid out the dimensions of the problem and the steps organizations need to take to begin to solve it. She contrasted the current state from the future goal and outlined how reward systems and the silo mentality will need to change to reach it.

This is not meant to say in any way this is how we are going to do it. This is really to try to stimulate some talk around how do we do this. What does it mean to industry? What are people thinking about? I probably won’t answer all your questions.

Knowledge about our products and processes is gained everyday. We learn something everyday about both our products and processes. But how can we capture it, use it, share it, disseminate it, learn some more from it? And again it is a cyclical process. Organizations are expected to act on the knowledge gained throughout the network to improve products and processes – but how? We are a multisite, global company. How do we get that across the global network? And how do we gain that knowledge and share it and use it everyday? How do we manage knowledge so that we don’t have to rediscover it?

We have made plenty of antibodies in drug development at Genentech. I can’t even tell you the number that have gone through, succeeded or failed. We experience this every year. We learn something, we do lessons learned. We don’t apply it. We forget it. The next molecule comes in, we go, ‘oh yea didn’t that happen three years ago, five years ago. We saw something like that.’ We don’t want to rediscover things, year in year out.

So managing, sharing and benefiting from existing organizational and product knowledge is essential to facilitate speeding up the product development process.

**Current vs. Future State**

So if you think about what is the current state? This is my view of what the current state is. You have discovery, research. You have lots of people talking to each other. They are in their own little world, their own little silo, and they go, ‘okay it is time for preclinical development.’ They throw it over the fence, and then you have lots of people talking in that little silo. And then if the product gets developed it goes into clinical development, it goes into commercialization. There is no feedback loop back to research. And even within these silos, there are silos within the silos. So you can’t get the information. Or if you can get it, you have to know who to go to, or know somebody who knows somebody to go to.

So that is the challenge. If you think about a multisite manufacturing company like Genentech, each one of those little circles can also be a site. So how do you get manufacturing information or technical information you learned during commercial manufacturing across the sites? How do you share best practices? How do you get that information across all of the manufacturing sites?

For the future state, our question is can we create an environment where we benefit from the collective experience and knowledge? Can we capture the knowledge created in interactions? We are having an interaction right now. How do we capture that knowledge? Provide people with the content and knowledge that they need in the moment they need it?

So that gets back to that lessons learned kind of concept. We do that all the time. We say, ‘we have a big project. We will do lessons learned.’ It is pretty Powerpoint presentation. It goes into some folder, and there it sits. It is never looked at again, or never thought about again.

It needs to be in the moment. You need to be able to access that knowledge when you need it. And in the absence of content, provide visibility to others who have relevant experience. You have to know who has the knowledge or who has experience around what maybe your issue is that you are dealing with today.
Hierarchies, silos and linear processes don’t meet this need. You have to have a network. It can’t be that traditional linear organization where you have your director, manager and your little worker bees underneath it and they don’t talk to anybody. You have to have feedback mechanisms. You have to have a ‘loopy’ network instead of a linear network. And then these people in the network have to believe that they are adding value.

**Reward Systems Need Changing**

So we have been talking in Genentech about what does our reward system look like. What do we reward our employees for? We actually are enabling the wrong behavior. Because if somebody comes in and says, ‘I can solve this problem,’ we go, ‘great. Here is a bonus for you.’ And then the next time a problem comes up the same person says, ‘I can solve your problem.’ Because the knowledge is now power and it is also rewarded.

What you want to do is set up a reward system that rewards benefiting the whole. So it is not activity-based. It is value-based. Have people added value? This is a big cultural shift for any company.

Intellectual capital is the sum of everything everybody in the company knows that gives it a competitive edge. That is what we are talking about here.

I love this HP quote: ‘If only HP knew what it knows, it would make three times more profit tomorrow.’ What we need is non-linear models that connect relevant people independent of their role. Again, it is ‘forget about what your role is. How are you contributing to the whole?’ You have to focus on product and process success. Every interaction is an opportunity to improve the next interaction. So again, you are leveraging every single interaction you are having.

**From Silos To Integration Networks**

Integration – acknowledging how things really get done: That is sort of like an elephant in the room. We don’t really want to talk about the fact that we have silos across the organization, and silos within the silos, and silos among the manufacturing sites. We have to understand the relationships and the network.

So part of what we are working on right now is to say, ‘what is our network? Or what could the network be? Should we focus on knowledge management of a product or knowledge management of processes, or both?’

Continuously improving the relevance of our interactions: You want to make sure again, ‘does it add value to the whole? Does it contribute to the whole?’

And unbounded networks: One of the things we have been talking about as well is, ‘this is my network, but I am constraining it.’ There could be people outside of what you normally think your network is. It could be customers. It could be your salespeople. People don’t think about sales. They have knowledge about your product.

The other thing is when I think about knowledge management, I have probably ten, fifteen years in the medical device industry. Knowledge management in the medical device industry is known as your ‘design history file.’ It is how you designed that medical device. Why should we try to recreate the wheel here? How can we leverage that kind of model? Maybe we can generate a product specification file like they have for European requirements.

Notice I didn’t say anything about an IT solution here. Because you really have to set up your architecture first. You have to know what you are going to tap into before you can even think about your IT solution.
So I have a very eager employee. He is working on this with me. He says, ‘we should set up a Wikipedia page. We should use Google.’ I respond that ‘you are going to the solution already. We don’t even know how we are going to set up the network – what the network actually is.’

**Requirements for Success**

- **Content** – what is the flow structure and context?

- **Culture** – what are the values? What is your reward system? Don’t set up any hero criteria. And they have to want to contribute. They have to care. People have to want to share their knowledge.

- **Process** – the work flow and timing; closed loop, double loop. Again it is not linear. It doesn’t go from A to B to C. And then it becomes part of your everyday job. You know that you have to contribute to the knowledge of the whole.

- **You have to have technology or infrastructure.** So is there a way to use your IT solutions so it is fast? They can tap into it. They can get an answer quickly. Think about when you call your IT help desk. Back in the eighties when computers first came out, there was no help desk. And if there was a help desk, it took hours to get you the answer. Now you can hear typing in the background. They have web-enabled themselves to tap into the knowledge for problem solving. It is the same kind of thing. How can you set up the infrastructure from an IT solution so you can get those answers quickly.

- **And then activity vs. value:** Again, don’t reward based on the fact that I am tapped into a hundred times in a year. It could be one time, but the knowledge that I share is phenomenal. So that is that reward system. Make sure it matters.

This is sort of a **framework** of how we are thinking of setting up implementation for knowledge management: You are identifying key staff groups. You do a needs analysis, because each of those groups in the network will have different needs, different knowledge needs. There will be organizational issues. There will be roadblocks. You have to plan how to get past that. And then we are going to make recommendations and have strategic impactful initiatives in order to implement this.

You can’t do this in a month. We have talked to people that have done knowledge management for IT and they said that the minimal time it takes is 18-24 months, because it is a cultural change. It is a paradigm shift in the way companies think about knowledge.
International Pharmaceutical Quality places its readers “Inside the Global Regulatory Dialogue”™ where the initiatives that will reshape the landscape are being defined.

Each issue provides an in-depth, cutting-edge report on a key focal point of concern – so readers understand the forces that are driving the industry/regulator dialogue and the emerging solutions that are being proposed. IPQ provides the context, analysis and insight needed to respond to and impact these pivotal quality regulatory trends and developments and make informed decisions.

IPQ is available either through individual subscriptions ($1,000/year) or site/organization-wide licenses.

Your Subscription Benefits:
• 12 monthly issues of IPQ
• Unlimited on-line access to IPQ’s valuable archives is included for both individual subscribers and license holders.
• online access to breaking news & alerts

To order use this form or go online to IPQpubs.com.

Site Licences— Call Rich Messmer at 540-246-3923 IPQ encourages you to contact the appropriate decision maker in your organization to take advantage of the added value and cost-effectives of a site/organization-wide access license. But don’t wait to subscribe —individual subscription payments will be deducted if/when a license is obtained.

100% NO-RISK SATISFACTION GUARANTEE:
Subscribe today. Go back to work and apply what you learn reading IPQ. If at any time during the life of your subscription, you’re not absolutely satisfied with its value and usefulness, we will immediately refund the unused portion of your subscription fee.

Don’t Miss the Next Issue of IPQ! Get Your Subscription Today!

The regulatory paradigm for pharmaceutical quality is undergoing a major transformation. Keeping up with this transformation is critical to your job and the success of your organization.

About Bill Paulson, Editor-in-Chief
Before launching IPQ in September 2007, Bill served for over two decades as the primary author of “The Gold Sheet.” During his career tracking the drug and biotech quality regulatory process, Bill’s identification of key issues and problem areas and emerging solutions has been influential in the targeting of resources by industry and regulators and has impacted the dialogue on the shaping of new CMC and GMP policies. More recently, Bill’s analysis in IPQ has provided key insight into the principles and practical implications of the international effort to evolve and harmonize the quality regulatory paradigm.

Paulson@IPQPubs.com • 202.841.5027

Subscription Order Form

☐ Yes, I want my subscription to IPQ started immediately.
Name ____________________________
Title ____________________________ Company ____________________________
Address ___________________________________________________________________
City ____________________________ State ______ Zip ________
Phone ____________________________ Email ____________________________

Payment Term
☐ 1 year for $1000/ year ☐ 2 years for $1750 (save 25% on your 2nd year)

Payment Method
☐ Check enclosed for __________ (Payable to IPQ Publications LLC)
☐ Purchase Order ____________________________
☐ Credit Card □ VISA □ MasterCard □ American Express □ Discover
MD residents please add 6% sales tax
Credit Card # ____________________________ Exp.Date __________
Name on Card ____________________________
Signature ____________________________

Please send to: IPQ Publications LLC, Subscription Dept.
7920 Norfolk Ave Suite 900, Bethesda, MD 20814
Questions: Call Rich Messmer 540-246-3923 • FAX 301-913-0119

The regulatory paradigm for pharmaceutical quality is undergoing a major transformation. Keeping up with this transformation is critical to your job and the success of your organization.