

# Practical Applications of Quality Risk Management

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Implementing a formalized quality risk management (QRM) program offers many benefits to industry and regulators. QRM allows a systematic approach to risk assessment (RA), incorporating it directly into a quality system, and provides the infrastructure (policies, standards, tools, and so on) to create a meaningful and sustainable program. ICH Q9 provides the framework for implementing QRM as a holistic program throughout a product’s lifecycle (1).

*Risk management* is not synonymous with *risk assessment*. Per ICH Q9, risk management is “the systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk.” QRM is a living process and must be managed throughout the lifecycle of product, process, or system. Risk management involves four steps: risk assessment, risk control, risk review and monitoring, and risk communication.

The focus of the July 2009 CMC Strategy Forum was the RA step. ICH Q9 defines *risk assessment* as “a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.” For several years the



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biopharmaceutical industry and several regulatory agencies have actively worked with qualitative and/or semiquantitative RA methods (e.g., failure modes and effects analysis, FMEA, and preliminary hazard analysis, PHA). This CMC Strategy Forum was designed to provide attendees with a greater understanding of how RA is applied throughout biopharmaceutical development and manufacturing — and also how risk management results are used both internal to a company and in its communications with regulatory agencies. This was accomplished with presentations and case-studies from regulators and industry as well as hands-on exercises illustrating key concepts.

## SECTION 1: CURRENT INDUSTRY RA PRACTICES

The morning of 27 July 2009 featured

presentations by Richard O’Keeffe (“Quality Risk Management: Industry and Regulatory Pulse Survey Results”) and Dan Weese (“Overview of Risk Assessment Methods and Applications”) of Amgen; and by Keith Webber (“Quality Risk Management from Concept to Practical Strategies”), Terrance Ocheltree (“The Role of Quality Risk Management in New Drug Development and Manufacturing: Findings from the ONDQA Pilot Program”), and Patrick Swann of FDA’s Center for Drug Evaluation and Research (“The Role of Quality Risk Management in New Drug Development and Manufacturing: Biotechnology Products”).

### Current Industry and Regulatory

**Trends:** To get a pulse on QRM trends within the industry and regulatory agencies, the CMC Strategy Forum planning committee designed and sponsored a survey before the conference. The 80 survey respondents represented 29 companies and regulatory agencies. O’Keeffe opened the conference by reporting on the survey results. His key theme was that industry and regulatory knowledge and understanding of QRM is evolving. Four in ten of company respondents said their organizations were in the development stages of a formalized QRM program; only 9% hadn’t started ICH Q9 implementation. Responses also indicated that the industry would like

more information about which tools to use in different situations, and that alignment among guidance from different regulatory agencies is important.

**From Concepts to Practical Strategies:** Webber presented for Gregg Claycamp on “risk-scientific” implementation of QRM concepts. Although risk is intuitive to everyone, application of that intuition to complex problems is not easy. Several RA tools provide a risk score; however, that does not equate to the actual “risk” and should not be represented as measuring it. Risk scoring methods are mostly about prioritization under a consistent process and do not constitute a “quantitative” assessment. They also drive consistent decisions within a quality management system. Webber discussed the importance of expert judgment during scoring and how “group think” can contribute to risk assessment outcomes.

**Types of RA Tools:** Because the focus of the forum was practical application of risk assessment, Weese presented an overview of available RA tools, including their strengths and limitations. Risk assessments are not easy to perform; appropriate training and expertise are needed for their execution. In choosing a tool, it is important first to thoroughly understand the purpose and desired outcomes of a risk assessment.

RA tools vary in their approach and level of rigor. A tool must be appropriate to the objectives of the assessment and the criticality of what is being assessed. It was noted that risk assessments can be both formal and informal; they may also take the form of a narrative or be performed using scoring tools. Typically RA starts with a top-down, broader-scope tool (e.g., PHA or risk ranking and filtering). Next, more focused and sophisticated assessments may be performed as needed using detailed tools (e.g., FMEA and hazards analysis and critical control points, HACCP).

Some more familiar RA tools include risk ranking, HACCP, hazard operability analysis (HAZOP),

## THE CMC STRATEGY FORUM SERIES

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

FMEA, PHA, and fault tree analysis (FTA). Most tools are intended to be prospective and use predefined ranking/scoring criteria and risk acceptance thresholds. Most also use impact/consequences and probability as their main considerations in risk scoring. The score for each risk identified using a qualitative or semiquantitative tool is typically a simple multiplication of its scores for impact/consequence, probability of occurrence, and sometimes likelihood of detection. It was also noted that tools are often customized to fit specific needs. For example, depending on the level of information available, a PHA may or may not include the detection score.

Before selecting a tool for RA, it is important to clearly understand your objectives, scope, and assumptions. A trained facilitator and the “right” multidisciplinary team of experts are also critical to creating a meaningful assessment and ensuring the appropriate risk management decisions. The facilitator must be both an expert in the particular RA tool and trained in group facilitation. RA participants should be trained in its

use, scoring criteria, and key assumptions for the assessment. Clear definitions and scoring criteria are especially important because there will always be subjectivity in a nonquantitative assessment, but the objective should be to make that assessment as standalone as possible, with supporting information and rationale for the scores adequately documented within it.

The FDA’s perspective on QRM application to new drug development and manufacturing was presented by Terrance Ocheltree — learnings from the Office of New Drug Quality Assessment’s ONDQA’s quality by design (QbD) pilot program — and Patrick Swann (the QbD pilot program of the Office of Biotechnology Products, OBP).

Overall, reviewers participating in the ONDQA program found risk assessments to be very useful. They were a central theme among submissions, with different tools used for different purposes. For example, some companies use FMAs during development to link process inputs and outputs to critical quality attributes (CQAs). Ocheltree also described several improvements that could be made based on deficiencies found in those pilot filings: The scope, outcomes, and decision making process for risk assessments should be clearly defined and well thought out to ensure that risks and decisions are understood, addressed, and explained adequately. RAs should evaluate interactions between multiple inputs and outputs, which was found to be a limitation in the ONDQA filings. Although detection of a risk may not constitute control, it does offer an important prioritization mechanism and should be assessed during development of a control strategy. Risk assessments should be integrated across a product’s lifecycle and include raw materials, equipment, product, and processes. And finally, it is important to address how RAs will be used to handle future changes.

Swann discussed how QRM can be integrated into a QbD approach throughout process development, characterization, validation, and

monitoring for biotechnology products and processes. Examples illustrated how different companies used different RA tools (risk ranking and filtering, FMEA) to identify CQAs in OBP QbD pilot program proposals. Most of these assessments included considerations of the impact of an attribute on safety and efficacy including pharmacokinetics and immunogenicity. Some included toxicology data, results from in vitro biological activity assays, and pharmacodynamic endpoints as part of attribute assessment.

After their presentations, the presenters participated in a panel discussion of current industry RA practices moderated by Joseph Siemiatkoski of Biogen Idec. Some questions addressed by this panel were as follows: What are the advantages and challenges of risk management? When is it appropriate to use a narrative RA rather than a semiquantitative/quantitative RA? What detail should be in a regulatory guidance? What RA tools have been successfully applied during product development, and what were the challenges? A summary of the key discussion areas is provided below.

Risk management is a valuable exercise to drive cross-functional and external communications, and it focuses resources and forces better understanding of product and process. Risk is conceptual and not easy to translate to a business program without considerable effort; subjectivity must be addressed, but over-standardization can be an issue. In general, the forum attendees would like more guidance and understanding about which tools are most appropriate to use for what applications. More discussion around how to deal with the subjectivity of risk assessments would be quite beneficial. Both industry and regulators agreed that better crafted guidance in these areas would be highly valuable.

## SECTION 2: OPERATIONAL DETAILS

After the morning warm-up presentations and discussions, the afternoon of 27 July 2009 was set up to engage the audience for hands-on

experience with performing risk assessments. The purpose of these exercises was practical demonstration of the benefits, challenges, and application of risk assessments. These exercises provided substantial background and training in RA approaches, scoring principles, and facilitation challenges while highlighting the importance of team structure and group dynamics.

The first exercise was a “fishbowl” to take preidentified participants from industry and regulatory agencies through a risk assessment in front of the conference attendees. A hands-on mock RA followed, with the conference attendees divided into four groups.

The unique hands-on format was very successful not only in highlighting benefits and challenges of QRM practical application, but also in teaching attendees which fundamental concepts and behaviors are absolutely essential for performing effective risk assessments. The shared experience also highlighted in practice that RA is not equivalent to risk acceptance or risk management — and that development and deployment of a successful risk management program requires trained and dedicated individuals. Each of the four group assessments involved identical starting materials. All participants gained insight into what parameters can affect scoring and outcomes.

**Fishbowl Exercise:** A panel of experts from industry, the FDA, and Health Canada was facilitated by Emabelle Ramnarine of Genentech through PHA for a prefilled syringe filling operation. The experts for the fishbowl session were Andrew Donnelly (MedImmune), Matthew Hilton (Eli Lilly and Company), Patricia Hughes (FDA-CDER), Suzanne Kiani (Genentech), Ingrid Markovic (FDA-CDER), Richard O’Keeffe (Amgen), Stephanie Pluschkell (Pfizer), Anthony Ridgway (Health Canada), and Joseph Siemiatkoski (Biogen Idec). The objective of this exercise was to familiarize the audience with key RA application concepts.

Ramnarine opened up the session

by orienting the team and audience to how a PHA is performed, including scoring criteria and ground rules for the working session. PHA was selected because it is a top-down RA tool that can be used with minimal data to understand high-level hazards and harm for an operation, process, or equipment. It is often a precursor to further in-depth analysis using another tool.

As emphasized above, it is crucial that all members of the RA team understand the scope of their assessment, inputs and outputs, assumptions, and RA terminology, and that their facilitator is experienced in guiding a team objectively. For purposes of these exercises, standard PHA definitions were explained to the team to ensure consistent application:

- *Harm* is damage to health including that which occurs from loss of product quality or availability (1)
- *Hazard* is a potential source of harm (1)
- *Hazardous situation* describes circumstances in which people, property, or the environment are exposed to one or more hazard(s) (2)
- *Severity* is a measure of the possible consequences of a hazard (1)
- *Probability* is the extent to which an event is likely to occur (3)
- *Risk* describes a combination of the probability of harm and the severity of that harm (1, 4).

The fishbowl exercise involved a filling operation for single-use prefilled syringes (PFSs). It was assumed that operation occurs in a Grade A room using a conventional filling operation without restricted-access barriers or isolators; that multiple needles do the filling; that siliconized tip caps and plungers are clean and inserted into the siliconized syringe bodies; and that the formulation is a clear, colorless solution (not a suspension). Product quality attributes included sterility, particulates, fill volume (head space), protein concentration, aggregation, and integral functional units. Process inputs included a compound solution, integrity-tested filters (tip caps and siliconized plungers), components



(siliconized syringe glass bodies), presterilized line parts (filling needles), qualified inspectors, and fill speed. Scoring criteria and a risk acceptance matrix were predefined for the RA exercise (Tables 1 and 2).

Concerns that the scenario might have been too hypothetical for a good discourse were quickly dispelled. The forum attendees were provided with a good example of just how intense and disordered risk assessment can become. The importance of a skilled facilitator became obvious because the panel required frequent refocusing to complete its task. The value of clear definitions for severity and occurrence became particularly clear during this exercise.

#### Group Risk Assessment Breakout

**Sessions:** After observing the fishbowl exercise, all forum participants divided into four groups of about 40 people each (predetermined by colors on their name badges) to attempt a PHA themselves. Each group was larger than a typical RA team (generally no more than 10–12 members), but these working sessions were designed to be managed appropriately. Each group was led by a trained facilitator, and a scribe was assigned to capture detailed observations that would be summarized for the next morning.

All four groups started with the same information. Their exercise was to evaluate a large-scale production bioreactor in a new facility, and the objective was to determine whether a company's controls were sufficient to support a new monoclonal antibody process. It was assumed that the company has good prior experience and knowledge of antibody processes and that the PHA was being used as a filter before doing a detailed FMEA. Process inputs included duration, media, dissolved oxygen, pH, temperature, and agitation. The process output was the production culture from the bioreactor. Quality attributes included product identity (the team had to determine how to define *identity assessment*, such as through amino acid sequencing), titer, glycosylation, product impurities (particularly aggregates), process impurities (particularly host-cell

**Table 1:** Explanation of risk scoring criteria used for risk assessment exercises

Score	Severity	Probability of Occurrence
1	No impact on product quality	Remote (no history of failure) ( <i>extremely unlikely</i> )
3	Does not affect quality but deviates from current procedures and requires justification; includes cosmetic or minor defects that lead to some customer dissatisfaction; corrective action may be needed	Unlikely (only isolated incidents of failure observed)
5	Potentially compromises product quality; further investigation or action is needed to confirm quality before release; lot flag(s) may be required	Occasional (failure is probable and has been observed)
7	Process results and/or product does not comply with specifications; results in product rejection	Likely (failure will occur in most circumstances; repeated failures observed)
9	Process failure potentially affects product, safety, identity, strength, purity, or other critical quality attribute	Frequent (failure is inevitable; consistent failures observed)

**Table 2:** Risk acceptability matrix used for risk assessment exercises

		Probability of Occurrence					Risk Scores:
		1	3	5	7	9	
Severity	9 Catastrophic	9	27	45	63	81	NAC (red) = unacceptable, intolerable  ALARP (yellow) = reduce risk to as low as reasonably practicable;  AC (green) = acceptable
	7 Critical	7	21	35	49	63	
	5 Serious	5	15	25	35	45	
	3 Significant	3	9	15	21	27	
	1 Negligible	1	3	5	7	9	

proteins), and contaminants (e.g., adventitious agents). Risks were again scored and prioritized according to Tables 1 and 2, but acceptable risk scores were not identified — which led to some interesting comments and questions about risk ranking and cutoffs between acceptable and unacceptable risks. Definitions were the same for these groups as for the fishbowl session.

The next morning, the group scribes and facilitators reported on each group's results and lessons learned. Although no two groups produced identical results, many conclusions were similar, and one overall conclusion was the same: that risk assessments are hard! The roles of facilitator and subject matter expert (SME) were further discussed, with general agreement that a skilled facilitator and "thoughtfully selected" multidisciplinary SMEs are critical to a good RA. The skills required for facilitation often require substantial training. A facilitator has to be a highly effective teacher, not only expertly familiar with the risk assessment tool and risk management

process, but must also have effective "soft skills." The facilitator is responsible for making sure the group understands the RA terms and parameters, for keeping discussions on track, and for steering the participants away from "group think." If the facilitator is also SME, then he or she must be careful not to unduly influence the group. The facilitator also needs to be able to encourage less vocal participants and curb those who, as one group put it, "like to hear themselves talk."

More than one group mentioned that PHA can be a conceptually difficult tool for scientists who are detail-oriented — especially for those familiar with using FMEAs. The ability to detect a consequence or a cause was raised during these discussions. Because PHAs are often completed early in a product lifecycle (when process experience is low), detectability is not typically included, which caused some consternation among participants. If a PHA is conducted later when more information is known, then it can be "customized" to add detectability.

Once risks have been assessed, a decision must be made to reduce them further or accept them. The topic of risk acceptance generated several questions and discussions among all the groups. Some came up with slightly different parameters from those in Table 2 for risk control and acceptance. For example, one group decided that no item with a 7 could be considered acceptable. Another group made the observation that “not all 9s are equal.” It was generally agreed that high-severity risks should be further evaluated even with moderate probability of occurrence.

The groups had to be reminded that this RA was focused on the product from the bioreactor, not on the final product. In one case, inoculum was explained as an input rather than a step to be assessed separately. There was some confusion as to scoring “severity of harm” or “severity of hazard,” and facilitators had to reinforce repeatedly for most groups that severity always must be scored for the harm (not the hazard).

One note of caution was shared: When you begin to get really efficient, it’s probably time to quit for the day because that is a potential indicator of a tired team being influenced by “group think.” Some groups confessed to getting quite “efficient” as time for the exercise began to run out.

**Case Study on Evolution of Multiuse Controls:** Next, Julia Edwards of Genentech presented her company’s approach to multiuse operations (multiproduct, new clinical product introduction, and multihost manufacturing operations). She shared the substantial evolution of QRM over time. Implementation at Genentech allowed for the development of consistent risk-based approaches across a network of drug substance facilities and products. Another example showed how RA tools can be customized to account for cross contamination. A customized FMEA was developed to support multiuse risk assessments by identifying where touch-points between contaminants and people, equipment, and/or materials can migrate throughout a facility. Finally, the case study demonstrated how QRM can be successfully leveraged in a regulatory submission.

That case study generated robust discussions on the value QRM can bring not only in addressing multiproduct risks, but also in facilitating regulatory submission strategies such as expanded change protocols (eCPs). Presentation of a detailed practical application of QRM led to detailed discussion of how it is leveraged at Genentech, including elements of the approach that drive consistency across sites, products, and situations. The ability to make consistent, transparent, and science-based decisions on risk control allows the extension of QRM to regulatory submissions. These concepts were further developed during the panel session that followed.

To close out Section 2 of this conference, Patrick Swann moderated a panel of the scribes and facilitators from the working sessions through a discussion on the operational aspects of RAs. This panel included Julia Edwards (Genentech), Matthew Hilton (Eli Lilly), Ingrid Markovic (FDA-CDER), Vince Narbut (Biogen Idec), Anthony Ridgway (Health Canada), Krista Terry (Genentech), and Dan Weese (Amgen). Some specific questions they

addressed included the following: What value does risk management provide? How do you ensure you have the appropriate RA team? How do you standardize across RAs (consistent risk control and risk acceptability decisions)? How do you keep RAs alive, and how do you integrate them into your routine operations and quality system? How do you evaluate product quality against patient safety and severity against process consistency (e.g., is heterogeneity a product quality or patient safety issue)? Is lack of process consistency that doesn’t affect patient safety still considered a high risk? How much detail do you document in your RA as opposed to in a risk management report? How would you document the decision making process in terms of risk control options considered and selected?

**Value of QRM As a Holistic Program:** Again, *risk assessment* is not synonymous with *risk management*. To be effective, risk management must be a holistic program that encompasses the whole product and process lifecycle. Not all potential benefits that could be gained from QRM yet have been realized by industry and regulators. An effective risk management program could enable a company to focus resources appropriately, which provides better understanding of both product and process by identifying gaps in knowledge about them. Risk management can make process, formulation, and analytical development more efficient, improving both product quality and process robustness. It can also be a valuable exercise for driving cross-functional and external communication.

Appropriate QRM implementation will improve control strategies. Risk control is the process through which decisions are reached and protective measures are implemented for reducing risks to patients (or maintaining risk within acceptable levels). A company’s risk management program will also define and hold corporate management accountable for “accepted” risks. Risk management can reduce cost through cost avoidance, but it may save money in other ways too. A good risk management program can lead to better design of new facilities, reduced validation, lower method failure rates, and reduced testing. It may also guide decisions about when to revalidate or periodically review — and whether product complaints warrant mitigation.

Risk is conceptual, however; it may not be easy to translate to a business program. Acceptance of risk remains a challenge: Who decides whether a risk is acceptable? How is that decision recorded? Risk reduction and acceptance form the second step of a QRM process: risk control. ICH Q9 defines risk acceptance as “the decision to accept risk” and risk control as “actions implementing risk management decisions.” Risk reduction and risk acceptance are iterative steps and must result in a documented decision either to reduce risk or acknowledge it to be “as low as reasonably practicable” and cannot be reduced further. Subjectivity remains challenging, but overstandardization can reduce the value of RAs to nothing more than an exercise. If overdone, RAs can become tedious, lose focus, or become too complex to be of value, so it’s important to evaluate “where to draw the line.” RAs can be team- or

expert-dependent and may not be meaningful to subsequent groups unless well documented.

The value of QRM to industry and regulatory agencies is likely to require further discussion. A rigorous RA process may result in diminishing returns if overleveraged. Given significant time and resources to support QRM, it is important to apply the ICH Q9 principle that RA rigor should be commensurate with the criticality of what is being assessed. Flexibility should be adopted in RA tool selection so that a chosen tool is appropriate to each situation. Appropriate application should be carefully considered to maximize the value of the RA exercise. The full value of QRM will be realized as it becomes fully integrated into a quality system.

**Team Dynamics and Role of the Facilitator:** To ensure the best possible RA team, you need to understand the objectives and scope of your risk assessment and the type of tool that would be appropriate. Team members should be selected for their level of relevant expertise. Use people with on-the-job experience at different levels to ensure appropriate granularity. It's possible to have "rolling attendance," with different SMEs attending according to the subject at hand. To minimize personal bias, it may be advisable to have more than one SME in each discipline. Team members should be trained in advance.

The hands-on RA activities (fishbowl etc) are discussed in this section (2). It is the facilitator's responsibility to ensure that every team member's voice is heard. The facilitator needs to have sufficient understanding of the area being assessed to effectively guide discussion without influencing the team. It is advisable to have trained facilitators from among different work groups, including corporate and site people. It is also the facilitator's responsibility to be sure a group is not becoming "too efficient." RA sessions should be relatively short — an hour and a half to two hours — to prevent "group think" and team fatigue and to ensure sound decision-making. When a consensus simply cannot be reached, voting may help get a team back on target.

In working with a contract manufacturing organization (CMO), it is advisable to perform joint risk assessments, with both sites keeping appropriate documentation. A CMO should have in-depth documentation, with the product sponsor keeping higher-level details. For all RAs, documentation is critical to record criteria and rationale for risk scores, overall thought processes, and decisions. A data and document management system should be developed not only to ensure that risk management documentation is readily available, but also to enable those documents to be revised and managed appropriately throughout a product lifecycle.

**Standardization of QRM Practices:** Best practices around standardization and integration of QRM practices within a corporation and industry were discussed. As indicated in the survey results presented by Richard O'Keeffe in Section 1, most companies do not yet have fully integrated QRM programs. However, providing standardized guidance in the use of RA tools, templates, risk scoring

and acceptance criteria, standard operating procedures (SOPs), standards, policies, and so on may be extremely beneficial given the challenges of subjectivity. Risk management committees at individual site and corporate levels also can be beneficial in providing oversight and governance for QRM activities and to ensure escalation and review of risk management decisions at the appropriate management levels. Implementation of a system for cross-risk assessment review and continuous learning will drive consistency and efficiency. People participating in QRM activities must be appropriately trained on risk management principles and tools.

**Keeping It Alive:** ICH Q10 describes quality risk management as an enabler that is integrated throughout a quality system (5). As discussed in ICH Q9, QRM must be therefore managed as a living process, and RAs should be reviewed and updated according to a defined procedure.

Participants discussed the need to build into the quality system a program to review and update risk assessments. For example, risk management must be integrated as part of change control and/or when a nonconformance or deviation provides new data. It was also suggested that product and equipment RAs can be managed as living documents as part of the annual product review or equipment periodic reviews that ensure maintenance of a validated state. A corrective action and preventative action (CAPA) system can also be used to implement risk control measures.

The key to keeping QRM alive is to ensure ongoing assessment of the effectiveness of risk control measures. "Gates" can be established throughout a product or process lifecycle to indicate points at which risk assessments should be reevaluated and updated as appropriate (e.g., for a technology transfer, a gate for completion or review of an existing RA could be set before initiation of qualification lots). Industry will fully reap the benefits of QRM when a quality system is established that will enable integration of risk management into the quality system framework instead of being an add-on activity (5).

**Evaluating Product Quality and Patient Safety Risks:** Implementing the ICH Q9 requirement around assessing effects on patient safety was an area of considerable debate. Assessing patient impact can be challenging, especially early in development or upstream in a manufacturing process. Also, some quality risks may be directly associated with a patient impact, but others may not. It may be inappropriate to consider patient safety in all risk assessments; at times it may actually confuse the issue. Again, it is vital to understand and keep in mind the purpose of a particular RA. Documentation of boundaries, assumptions, and rationale is very important.

Several companies use impact on product quality as a more conservative surrogate for patient safety effects. This choice may be appropriate given the subject matter expertise of RA participants and challenges associated with accessing appropriate clinical data and/or knowledge to directly support determination of patient impact.

The FDA initially questioned that approach and



highlighted the importance of linking RAs back to patient safety. There was overall agreement, however, that we can use product quality as a surrogate for patient safety, especially when an operation upstream of the patient is being evaluated or direct impact to patients cannot be evaluated.

It was suggested during discussion that understanding of the links between quality attributes and clinical outcomes needs to increase. A good start would be to leverage preclinical, clinical, pharmacokinetic, and toxicology data. Mining of clinical trials data may also help link supply chain data to adverse events. Many clinicians are reluctant to use material that may compromise the outcome of a clinical trial, however, making such data mining important. It was noted that these activities may not be routinely necessary if product quality can be successfully used as a surrogate for patient safety.

Product quality expressed in terms of CQAs may be more relevant for process risk assessment. Understanding of patient safety is required in determining CQAs. Ideally, clinicians should be included in those determinations and in assessing associated risks. Later, data generated through development and characterization studies can be used for process RAs.

### **SECTION 3: A REGULATOR'S PERSPECTIVE — FILING WITH QRM**

The afternoon of 28 July 2009 was dedicated to presentations and discussions led by members from different regulatory agencies about how QRM is being applied for regulatory filings. Presenters included Patricia Hughes ("Application of Quality Risk Management Principles During Review and Facility Inspections") of FDA-CDER, Kevin O'Donnell ("Practical Strategies for Improving Quality Risk Management Activities in GMP Environments") of the Irish Medicines Board, and Nancy Waites ("The Role of Quality Risk Management in Manufacture of Biological Products: CBER Perspective") of FDA-CBER. Practical applications of RA were

highlighted, including incorporation of QRM in regulatory submissions such as eCPs. Additionally, QRM provides background information to reviewers on a sponsor's decision making process, allows regulators to focus on what is important during an inspection, and increases confidence in a sponsor's quality system.

Performing risk assessments is not a regulatory requirement in the United States or Canada, but it is in the European Union. Regulators noted that although a form FDA 483 would not be written for the lack of QRM, regulatory action could result from the lack of a controlled, systematic, and science-based approach to decision making.

The regulatory presentations were followed by Joseph Kutza (MedImmune) moderating a panel discussion with Terrance Ocheltree and Patrick Swann (FDA-CDER), Anthony Ridgway (Health Canada), and the three presenters for this section. Several questions were considered: What type of risk management information should go into different filings (IND, BLA, QbD or non-QbD)? For what applications is QRM being used effectively as part of the quality system or as part of a product lifecycle? How do you handle situations in which risk acceptance/tolerance levels differ between a company and the regulatory agency? What type of QRM training would be useful for reviewers/inspectors?

**What Goes Where?** Regulators generally indicated that summaries are more useful to them than are huge, detail-laden reports. Additional information (including actual data) can be put in an appendix for further reference. A few suggestions were made based on the regulators' observations during submission review and inspection. Control strategy should include RA of the critical process parameters (CPPs). Process controls are an important component of control strategy and (for drug substance) can be described in section 3.2.S.2.2 of a filing. RAs related to chemical impurities belong in NDAs, where they are mainly used in 3.2.P.2

(drug product pharmaceutical development), although some have been used for drug substance. They can also be included in the overall quality summary. For BLAs, risk assessments are useful in Section 2.6 for CPPs or (if related to validation) in the validation sections. Potential CQA information is developed for an IND and enhanced throughout development — and can be described in 3.2.S.3.1. As with NDAs, RAs can also be included in the quality overall summary (QOS). Risk can be applied separately from QbD: A non-QbD filing may include risk assessments. RAs should be included in a parametric release and any time you are reducing or changing testing.

**QRM Applications:** Several applications of QRM were noted by the regulators. These examples were shared to show participants where other corporations are effectively using it: in nonconformance and deviation investigations, in investigating complaints, in change control, in facility design, in determining product quality, in raw material control, and throughout manufacturing processes. QRM is also being used in process change submissions involving site-to-site transfers, changes within processes, transfers to CMOs, and other change situations. Bioburden control, container/closure changes, QbD applications for design space, and validation protocols have also made use of QRM.

**The Patient Wins:** The potential drawbacks of sharing RAs with regulators were also discussed. Industry's perception was that differences of opinion in risk acceptability decisions could lead to enforcement actions. What happens when a company makes a risk-based decision, and a regulator disagrees with that decision? "The agency wins" was heard from somewhere in the audience, followed by "The patient wins, that's the whole point" from somewhere else. Consensus among the regulators was that as long as decisions had strong supporting science-based rationale, they would not typically challenge risk scores. Industry was advised that a risk assessment may be

insufficient to support a decision, so additional data and rationale may be needed. As Keith Webber had pointed out during his presentation on the first day, “A risk score is not risk.” It’s not about the scores themselves, but about what you do with the risks that have been identified and scored.

Citations have been issued during inspection to companies that tried to use RAs to justify current practice or ignore obvious risks (e.g., to justify release of deviant batches without sufficient investigation). Most 483s, however, were issued because RAs led to improper actions such as inadequate validations or investigations (e.g., not using worst-case scenarios in cleaning validation). Disagreements over scoring often can be resolved by a company demonstrating well-documented supporting rationale, although in some cases the RA was insufficient to justify a company’s conclusions. Industry was also advised that RA cannot be used to get out of complying with a regulation. Enforcement actions may result from improper use of RA in such instances.

**Reviewer Training:** The FDA’s Division of Manufacturing and Product Quality has not yet received formal training in QRM, but the experience of inspectors and reviewers is growing quickly. The Irish Medicines Board also has no formal training yet, but its regulators take part in pharmaceutical inspection cooperation schemes (PICSS) to develop risk-based kits for inspectors. Anthony Ridgway indicated that Health Canada’s a risk management training primarily addresses a management perspective rather than manufacturing. CBER has some high-level internal training for inspectors and reviewers and is developing a new program for 2010. The training program of the Office of Biotechnology Products was used as training for the OBP pilot, but more is needed there. Some reviewers have prior (industry) experience in risk management, and the pilot programs provide further insight. It was pointed out that the experience of doing a risk assessment is a very valuable part of this training. Regulators

acknowledged that they do not have QRM-specific training programs in place, but would like to increase their level of understanding and training on QRM. They encouraged the industry to provide training sessions.

### WORTH THE TROUBLE

QRM can play a valuable role throughout a product’s lifecycle. Principles presented in ICH Q9 provide a forum for cross-functional dialog, documentation of decisions, and discussions that led to product quality or patient safety decisions. QRM can also lead to cost avoidance and savings in areas such as facility and equipment design, validation, and testing.

Establishing a structured QRM program facilitates a systematic approach for performing risk assessment, making appropriate risk acceptance and risk control decisions, and integrating risk management into the quality system. Use of standard policies, standards, SOPs, and other tools enables a consistent, meaningful, and sustainable risk program. A key follow-up topic for discussion would be development and deployment of a QRM program and integration of it into a quality system.

Risk assessments are not easy. They require skilled facilitation and appropriate, cross-functional team members. It is important to select the right RA tool and ensure that all team members are clear on the objectives, assumptions, scope, and definitions pertinent to the activity. It is in the best interest of a company to have standard terms, templates, and guidance for all risk assessments.

QRM is a living process, and RAs are living documents. They must be reviewed and revised as appropriate according to established procedures in change control, annual product review, revalidation, deviations, investigations, and so on. RAs can assist in development of risk-based regulatory submissions. They provide background information to reviewers about a company’s decisions and thought processes that went into them. Effective, well-documented risk assessments with robust science-based

rationales may increase agency confidence in a company’s quality system.

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