IPQ INTERNATIONAL PHARMACEUTICAL QUALITY
Inside the Global Regulatory Dialogue

Industry Paradigm Shift from Compliance to Quality Investment Value Urged at Dublin Summit

A "Quality Business Leadership Summit" (QBL), held in Dublin, Ireland in May 2024, brought industry, regulator and academic experts together to explore how to speed up pharma's progress from a compliance to a quality investment value modus operandi that better drives innovation, financial performance, and supply chain resilience.

At the summit, hosted by the Pharmaceutical Regulatory Science Team (PRST) at the Technological University (TU) Dublin, prominent leaders in the quality regulatory dialogue from the U.S. and Europe took stock of where the pharmaceutical industry is on this journey, where the constraints and hurdles now lie, and what needs to be done to make this "fundamental shift" a reality.

> **Emerging into relief was the need for industry, with regulator blessing, to take the lead in embedding quality culture into the highest levels of business decision-making – so that investment in quality management and systems is evaluated in terms of its ability to create value and produce resource savings rather than as a line-item budgetary cost to be minimized.**

The summit was designed around "Six Traits of Quality Business Leadership," with speakers and panel discussions addressing the traits in turn:

- lead the path to one global quality regulatory framework
- visibly demonstrate responsibility for quality
- advocate that quality is owned by all through developing senior management partnerships
- engage employees to continuously improve quality
- make risk-informed decisions that benefit patients, and
- promote quality as a value-driven financial advantage

Anders Vinther, chair of the summit and CEO of Quality Business Administration, noted in his opening remarks that the pharmaceutical industry has yet to fully achieve the vision – laid out in 2002 by former FDA Acting Commissioner Janet Woodcock in launching the "Pharmaceutical cGMPs for the 21st Century" initiative – of "a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drugs without extensive regulatory oversight."

Woodcock has continued her engagement with the issues of pharmaceutical quality since her retirement from FDA in 2024, including collaborating with Vinther in raising awareness of the need to further empower quality leadership.

At the summit they both stressed that quality leaders need to acquire the necessary communication skills to engage with company executives and secure the investments necessary to drive a robust quality culture – and that when properly integrated, quality can provide a financial advantage rather than being seen solely as a regulatory obligation.

[Editor's Note: For other recent IPQ coverage of the current regulatory dialogue on evolving the quality paradigm in pharmaceutical operations see:

- *IPQ September 25, 2023, which draws from a PRST meeting on the ICH Q9 revision in reviewing the heightened focus on integrating knowledge into risk-based decision-making to enable improvements in quality and reduce drug shortages*
- *IPQ February 20, 2024, which focuses on the challenges of and drivers for this shift from a compliance-oriented mindset to one based on a control strategy embodying the risk management principles of ICH Q9(R1) as the complexities of processes, products, and big data handling continue to expand, and*
- *IPQ May 31, 2024 on the continued realization of the 2003 ICH "Quality Vision" goal of evolving its quality guideline series to keep pace with and provide support for technological innovation through the development of "a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science."]*

Summit Leads to a Manifesto for Change in Quality Business Leadership

A draft manifesto for quality business leadership was presented at the summit, with participants invited to comment.

Almost 200 comments were received during the meeting, which were used to shape a finalized manifesto. It calls for a transformation in pharmaceutical quality management – urging professionals to "be bold and aim higher" and to move beyond mere cGMP compliance and embrace a more proactive, strategic role and transition the Quality organization from a support function to a business partner. *[See below.]*

QUALITY BUSINESS LEADERSHIP MANIFESTO

Redefining Quality Management in the Pharmaceutical Industry

The pharmaceutical landscape is constantly evolving with medical breakthroughs and technological advancements. Yet, our quality management systems often struggle to keep pace, particularly in the face of concerning global medicines shortages.

Beyond Compliance: A New Definition of Success

Simply meeting cGMP regulations is no longer sufficient. We envision a future where quality management transcends regulatory requirements, becoming a strategic cornerstone for business growth.

Introducing the Quality Business Leader

This vision demands a new kind of leader: the **Quality Business Leader**. These leaders possess a deep understanding of both quality and financial principles, championing:

- **Patient-Centric Focus:** Every decision prioritizes patient safety and well-being. Rigorous benefit-risk analysis ensures patients have consistent access to safe, high-quality medications.
- **Leadership by Ownership and Partnership:** Quality becomes a shared mindset, nurtured at all levels across the organization. Leaders foster collaboration and a sense of ownership for quality excellence.
- **Regulatory Collaboration:** We advocate and lead the path to a streamlined, global regulatory framework that encourages continuous improvement and innovation, including the implementation of new ideas and technologies.
- **Streamlining for Efficiency:** Quality management systems and processes are simplified for enhanced effectiveness, agility, and full integration into the overall company business. Every step in the supply chain is optimized for the highest quality outcomes.
- **Financial Advantage Through Quality:** We achieve sustainable financial success while upholding the highest quality standards. Quality management becomes a value that drives business prosperity.

The Quality Organization transitions from a Support Function to a Business Partner and the Quality Business Leader ensures sustainable product quality, consistent product supply, and robust company financial performance.

A Call to Action

We are driven to disrupt the current state and forge a new path. The time for action is **now!** Achieving this vision demands changes to how we operate and an unwavering commitment from everyone involved. Remember, every revolution begins as a vision, an idea taking shape in our minds before becoming reality. This is where it starts.

Let's unleash the power of quality – are you in?

The summit discussions and findings have also shaped the development of a new postgraduate course leading to a "Certificate in Quality Business Leadership," accredited by TU Dublin.

The 10-week online program, launched in the fall of 2024, is designed to "transition quality and other key leaders into quality business leaders who make the quality function a core company business competency." The curriculum, built around the six quality business leadership traits, provides training from senior industry and regulatory thought leaders, including Vinther and Woodcock.

A second course is planned to begin in late February 2025. *[A link to the course information is provided on p. 9.]*

HPRA's Nolan Leads ICMRA Efforts on Global Quality Regulatory Framework

Ireland Health Products Regulatory Authority (HPRA) Chief Executive Lorraine Nolan opened the summit with a keynote presentation on international collaborative efforts to develop a global quality dossier.

She described the progress of two pilot studies under the auspices of the International Coalition of Medicines Regulatory Authorities (ICMRA), as part of an initiative called the Pharmaceutical Quality Knowledge Management System (PQKMS).

The first pilot focused on a collaboration among global regulators in the assessment of CMC post-approval change management protocols (PACMP). A second pilot study, the collaborative hybrid inspection pilot (CHIP), aims to improve global cooperation in the inspection of manufacturing facilities.

Both pilots are important steps towards the "coordinated assessment of post-approval changes…and a single outcome applicable across all of the regions," with the ultimate goal of "one submission and one global approval."

Given the focus of the summit, Nolan opened her presentation with reflections on her personal journey as a quality leader and the success of the manufacturing industry in Ireland. She then provided background on ICMRA and the development of the PQKMS.

Nolan outlined the different facets and vision of building capability in two areas: ● the collaborative assessment and inspection processes and ● supporting digital and data infrastructure.

In closing, she outlined the future directions of the PQKMS project, urging pharma industry CEOs to support their quality leaders in "co-designing" future pathways towards a global quality dossier.

[A review of Nolan's presentation was provided in IPQ's May 24, 2024 Weekly Supplement. Included are her full remarks and slides. For more details and updates on the ICMRA pilots, see the Weekly Supplements for the weeks ending September 6, 2024 and December 6, 2024.]

Former FDA Leader Woodcock Points to Industry's Responsibility for Quality

In the second keynote speech, Woodcock began by acknowledging the ICMRA PQKMS work being led by Nolan in collaboration with FDA CDER Strategic Program Office Director Theresa Mullin ***(see IPQ December 6, 2024).***

Woodcock emphasized the potential impact of the "holy grail" of a single quality approval and the benefits of "reducing complexity and driving change and harmonization."

She reflected on her long tenure at the FDA, quality challenges over those years, and her hopes for the future. In her discussions of the history of pharmaceutical quality in the U.S., she commented on a poster of quality she had in her office of the early days of inspecting aseptic manufacture compared to current expectations.

[Editor's Note: See IPQ February 28, 2022 for comments from Woodcock as she took on the role of FDA's Principal Deputy Commissioner, continuing her strong contribution to the effort in the U.S. and around the world in making drug and biologic regulatory processes as supportive as possible of manufacturing innovation. See also IPQ Aug 28, 2022 for a detailed review of an FDA-commissioned study spearheaded by Woodcock and carried out through the National Academies of Sciences, Engineering, and Medicine (NASEM) to drive the industry/regulator agenda on advancing innovation in pharmaceutical manufacturing.]

Moving on to quality at the turn of the 21st Century, Woodcock explained how CMC review became "increasingly detached" from inspections and how inspections and enforcement became a "cat and mouse affair," with industry's goal often being to pass FDA inspection.

"As far as an aspiration or ambition, that is pretty lame," and not the "agile, efficient, maximally effective" approach that she had envisioned. Helping prompt this mindset was that inspectors were "not fully aligned with the center staff," with industry often not getting a single message from the regulator – which "is a real problem." Before leaving the agency, she initiated a major reorganization, including how the inspectorate works and interfaces with the reviewing staff, in an effort to remedy that situation.

In describing the current state of pharmaceutical quality globally, she pointed to the "reputational hits" to the pharma industry associated with quality lapses – drawing comparisons to other industries and highlighting the potential damage to price negotiations in the U.S.

Woodcock closed her presentation by stressing that quality professionals "need to take a collective stand" and develop and publicize common objectives and principles. "Own this. Don't look to the regulators. It is not the regulator's responsibility."

Among her suggestions, reflective of the quality traits underpinning the summit, were: ● highlighting the business value of quality ● advocating for appropriate placement of quality leads within the corporate structure ● training quality professionals in corporate leadership, and ● developing "realistic options" for regulatory incentives.

[See pp. 11-16 for Woodcock's full remarks during the QBL Summit.]

ICH Q9(R1) Lead O'Donnell Weighs in on Quality Leadership and PQS

Also advocating for strengthening quality leadership and its relationship to the pharmaceutical quality system (PQS), HPRA Market Compliance Manager and Rapporteur for ICH Q9(R1) Kevin O'Donnell addressed the role of quality risk management (QRM) in helping industry leaders achieve their objectives ***(see IPQ September 25, 2023).***

Good quality leadership, O'Donnell posited, entails having an effective pharmaceutical quality system (PQS).

He supported his view with quotes from the European GMPs, including, critically, the requirement that "manufacturers must not place patients at risk," which follows from the lack of an effective, well-monitored PQS. The EU GMPs also underscore that "senior management leadership and their participation in the PQS is essential."

O'Donnell highlighted the current focus on PQS effectiveness, citing ICH Q12 product lifecycle management flexibilities and an appendix in ICH Q10 on the PQS, which refers to "optimised science and risk-based post-approval changes." He cautioned participants at the summit that "if companies just comply with the GMPs from a very minimalist perspective, they should not expect to get regulatory relief or flexibilities from regulators."

To illustrate the importance of appropriate risk-based change management, O'Donnell utilized two case studies: ● one demonstrating an effective PQS in a global biologics company, and ● another on a poor QMS at a contract manufacturing organization (CMO), where inadequate training and understanding of the critical role played by QC analysts resulted in major risks to patient safety.

[See pp. 17-27 for O'Donnell's full remarks at the QBL Summit.]

FDA's Friedman Reiterates Quality Business Synergy

In a recorded presentation, FDA CDER Manufacturing Quality Deputy Director Rick Friedman stressed the need for a strong partnership between quality and operations leaders in assuring a continuing state of control through vigilant lifecycle review and oversight.

Company executives, who are ultimately accountable for the quality of medicines, Friedman said, should enable this partnership by providing visible support for quality, a strong quality system, and the provision of needed resources.

In focusing on "quality/business synergy," he pointed to the "critical responsibility" of quality leaders in an organization to develop good relationships with top executives – and, in turn, for the executives "to be engaged and visibly involved in quality matters."

He noted that where those relationships are strong in companies, which is "usually manifested today with a CQO, Chief Quality Officer, who reports directly to the CEO," quality is integrated into business decisions, and the companies "tend to have stellar compliance records."

Friedman shared examples of how the FDA has been increasingly addressing management oversight and operations leadership responsibilities in warning letters over the last 10 years. One request to a firm was to "describe how top management supports quality assurance and reliable operations," including the timely provision of resources "to assure a continuing state of control."

He also emphasized the benefits of high-capability manufacturing processes and demonstrated how unreliable, low-capability processes create conditions for excessive variation in the quality of finished products. "Lower capability manufacturing operations will continue to receive extra FDA scrutiny," he affirmed.

[A review of Friedman's presentation was provided in IPQ's June 7, 2024 Weekly Supplement. Included are his full remarks and slides.]

Panel Discussion Addresses Changing Quality Culture and "Coopetition"

One of the big challenges addressed at the QBL summit was the "how" in changing a company's quality culture. Consultant and author Holger Rathgeber shared his experiences and suggestions for engaging employees as well as senior managers to lead change within an organization – a topic that was discussed further in a panel following the morning presentations.

Joining the speakers in that panel discussion, moderated by Vinther, was EMA Scientific Officer and Chair of the Inspectors Working Party (IWP), Brendan Cuddy.

The opening question asked if lessons learned from the airline industry could be applied to pharmaceutical quality management.

Panelists referred to recent adverse experiences at Boeing, with Woodcock describing how the incident highlighted that "quality needs to be owned" with a choice of either "internal vigilance or reputational decline." The importance of an effective PQS was discussed, which can prevent or detect such issues before they result in disaster, as well as the need for "really good communication between the industry and the regulator at the time of an incident so that it doesn't become a crisis."

Addressing how to quantify the financial advantage of quality, Woodcock noted that pharma's view in the past has been that "every aspect of the manufacturing industry is competitive, with everything buried in secrecy."

She encouraged a different approach, extolling the advantages of viewing manufacturing as a "shared technological activity" – challenging industry to ask, "What happened when we switched to better processes? How many defects did we prevent? How many batches no longer got thrown away?"

The ensuing discussion considered how to quantify the financial value of using advanced technologies such as continuous manufacturing and demonstrate how they can bring value to the supply chain. Quality managers need to ensure a continuous supply of medicines, Cuddy stressed. Patients "want medicines that are like electricity. They turn the switch, and their medicines are there. So that is your goal."

Nolan pointed out that changes in manufacturing tend to be one of the major contributing factors in medicines shortages. Further discussion centered around the importance of understanding and appreciating the personnel involved.

Reinforcing the messages from O'Donnell's case studies, Cuddy also cited the GMP principle that "the correct manufacture of medicines relies on people."

He commented that "if you are going to gain a competitive advantage, if you are going to ensure a continuous supply of medicines, you have to understand your people." Since the people on the floor are making daily decisions about quality and learning from each other rather than training programs, "you need to understand that and incorporate that into your risk assessment."

The discussion then moved to a consideration of company culture and quality management.

Rathgeber elaborated on how to change company culture from a "burning platform" to a "burning desire" perspective and described four core principles necessary for driving cultural change.

Panelists also discussed the concept of "coopetition' – i.e., competition through cooperation and collaboration. This led to a discussion on "culture assassins," i.e., those with an ingrained resistance to change and how best to address this issue.

[See pp. 28-35 for the full QBL morning panel discussion.]

Panelists and QBL Summit Organizing Committee

Front row (panelists): Kevin O'Donnell (HPRA), Janet Woodcock (formerly FDA), Lorraine Nolan (HPRA), Holger Rathgeber (Consultant), and Brendan Cuddy (EMA).

Back row (summit chairs/organizers): Anders Vinther (QBA), Anne Greene (PRST/TUD), Martin Lipa (PRST/JAPRS), and Colin Hughes (TUD).

Vinther Explains How to Articulate Quality in Financial Terms

In the afternoon sessions of the summit, the discussion turned to the industry learnings on the importance and benefits of senior management partnerships.

Vinther explained how to articulate needed quality improvements in financial terms to gain support and investment from senior management. As well as being based on his own extensive experience in leadership positions across major pharmaceutical companies – including Novo Nordisk, Sanofi, and Genentech – his presentation reflected input from Chief Financial Officers he worked with over his career.

Comparing the appreciation of eating a high-quality meal to a low-quality burger, Vinther commented that "for

quality for pharmaceuticals, we really only experience it when it is not there" – for example, in the case of shortages, adverse events, loss of batches and remediation actions after regulatory observations.

He acknowledged that "better quality" can be a hard sell within a company and that many senior quality leaders have to deal with daily issues rather than focusing on longer-term strategies to expand the quality role.

"What I think we have not been good enough at generally in our community of quality leaders is to use the quality system as that engine that drives not only quality improvements but also financial improvements."

He went on to explain how to translate from CGMP and quality risk management terms into the financial concepts of revenue, cost of goods, and labor costs to create a "financial risk score," which had helped him have a "fantastic" conversation with a CEO.

Turning to knowledge management, Vinther expressed his view that "in general, we are not very good at actively enabling" it. Pointing to the attrition of knowledge when people leave any organization, he stressed the importance of both institutionalizing knowledge and extracting knowledge from outsourced operations.

He went on to advocate for reducing the complexity of the quality system, and taking a systems thinking approach to operational excellence, rather than the current situation which, he maintained, "is focused on cost reductions. And many times, it is short-term cost reductions."

Vinther concluded by stressing that quality can be a value-driven financial advantage and that there is a "huge opportunity to enhance how we understand running a business. And it is not about quality only. It is about quality and financials. It is not one or the other. It is both of them that we need to think about."

[See pp. 36-45 for Vinther's full remarks at the afternoon session of the QBL Summit.]

Industry Experts Share Experience of Quality Leadership

In a complementary presentation to Vinther's, Alexion Global Head of Quality Operations Jane Wyatt shared her experience of proactive quality management leadership, using real-life case studies to demonstrate the financial value of quality. Since the summit, Wyatt has taken up a position as VP R&D Quality at GSK.

Following Vinther to the podium, management consultant Pat O'Mahony, who was formerly HPRA's CEO and chair of the EMA Management Board, shared his thoughts on the "six traits" of QBL – interspersing anecdotes from his extensive experience in healthcare leadership positions. ***[The full remarks of Wyatt and O'Mahony are available in the proceedings of the QBL meeting, a link to which is provided on p. 9.]***

A panel discussion on the importance of the partnership between the quality and operations functions in a biopharma company was moderated by Mallinckrodt Specialty Brands Quality and Operations Executive VP Paul O'Neill, who summarized the outcomes under the headings of: • governance • people, and • success measures ***(see next page).***

The engaging discussions gave summit participants an opportunity to reflect on the quality leadership skills demonstrated by the late Michael Kamarck, who oversaw development of the Wyeth Grange Castle Dublin biopharma manufacturing site in the early 2000s. In 2008, he became Technical Operations and Product Supply President for Wyeth, responsible for commercial manufacture of biotech and other products with yearly revenues of more than $20 billion, 25 international facilities, and 17,000 employees.

Accenture Managing Director Barry Heavey commented that Kamarck had "widened the lens" of partnering and encouraged connectivity with R&D, academia, codevelopers, and CMOs as well as across quality and operations functions.

Sanofi Global CMC Biologics Senior Director Meg Leahey, one of several QBL delegates who worked with Kamarck at Wyeth, commented that "what we did really well at Grange is partner with regulatory as well as with our MSAT [manufacturing science and technology] colleagues."

She explained how she took those learnings forward into subsequent CMC global regulatory affairs (GRA) roles in different companies, where she "encouraged and pushed to have those collaborations with quality, with MSAT, and with operations" for post-approval changes, because some team members "were actually not" up-to-speed on the operations side.

"As we moved forward into successful submissions and put together data sets, the GRA CMC people needed to collaborate with our quality, operations, and development people to ensure that 'widening the lens.' It is a cross-functional collaboration that leads to that success."

Quality's Role in Partnering with Operations

The following is a summary of the key concepts and take-away messages from the QBL Summit presented by the afternoon panel moderator Paul O'Neill.

Governance

- Design of Governance structure and Partnership through all levels of governance
- Shared partnership in:
  - Strategic Roadmaps in Quality/Ops *eg.*, Driving Innovation
  - Annual Goals
  - Co-Sponsorship of key initiatives
- Creating multi-functional governance that drives decision making at the right level
- Supports Programs/Projects/ Run the Business

People

- People aligned with the vision of partnership
- Having the right people in the right roles where their partners and leadership can fully trust and support them
- Cross-pollenating Talent pipelines between Operations and Quality
- Directly promoting cross functional working across Operations and Quality teams
- Fostering talent with unique talent profiles to bring unique perspectives

Success Measures

- It is defined, quantifiable and will be measured across functions
- Agreement in place in terms of defining and measuring what is success for dlellivering what our Industry's Patients need today and in the future
- Delivers speed and compliance
- Deliivers efficiency and compliance
- Has the belief and trust of the staff in terms of the value of this partnership

Business Confidence is Needed for ICH Q10 Product Realization

A final panel discussion, led by Janet Woodcock, included speakers from the afternoon session. *[The final panel discussion is included in the QBL Summit proceedings.]*

Drawing the summit to a close, Vinther acknowledged the efforts of the PRST and TUD, in particular Greene and Lipa, in organizing the summit and developing the QBL Certificate course.

He underscored the need for "moving quality not gradually, but a big step change from quality leadership to quality business leadership."

Pointing to the attention that the six traits underpinning the meeting have been getting in the last few years, Vinther commented that "a lot of it is common sense. But common sense is only implemented if you take the time to do it." Part of the reason for the lack of successful action to date is also that "it actually requires learning new skills."

Following Vinther's closing comments, AbbVie Global Quality Assurance Senior VP Sean McEwan gave a vote of thanks to him for being a "thought leader" and for highlighting the need for confidence in business language to achieve the "product realization" referred to in ICH Q10. *[McEwan's remarks are provided on the next page.]*

AbbVie's Sean McEwan on the Need for Quality Leaders to Have Confidence in Business Language

I have been in this job for six years, and I spent 22 years in manufacturing. Anders, I want to thank you for being a thought leader in this space because one of the things that I observe for quality professionals is that there is probably nobody more dedicated in terms of putting the patient first than a quality professional. I truly believe that. We don't get it right all the time, but we get it right 99.9% of the time.

But fundamentally, I think as business leaders, we lack confidence. And I think what you are doing here is legitimizing a framework whereby this will give quality leaders the business confidence to round out what it means to advance quality – and that is to make it everybody's responsibility, and to talk to the decision-makers and convince them that this is the right thing to do.

But it means that we have to exercise new muscles. It means that we have to learn new languages. It means – if you look at ICH Q10 – 'achieving product realization.' That doesn't mean anything to a CFO. But if you actually break it down, what it really means is getting the best out of your plants, the best out of your products, and having sustainable, high-quality products.

The patient will benefit. The industry will benefit. Everybody will benefit. And so, I just want to compliment you, Anders, in terms of persevering. You had an idea and have been able to actually bring people here. I flew in this morning from Chicago, and I am standing up here because I am tired.

I just want to thank you, Anders, for pulling this community together. It is not easy to pull together this kind of forum, so credit to you…and keep up [the good work]."

2025 Summit Will Assess QBL Implementation Progress

As a follow-up to the inaugural QBL summit, a second event is planned for May 16, 2025, hosted by the Ireland's National Institute of Bioprocessing Research and Training (NIBRT) in partnership with Quality Business Administration, TU Dublin, and PRST.

[An outline of the 2025 summit, shared by the organizing committee, is provided on the next page.. CLICK HERE for updates on the summit.]

LINKS:

- QBL 2024 Summit Information/Links
- QBL Certificate Program
- QBL 2024 Summit Proceedings in JAPRS

Quality Business Leadership Summit 2025 Outline

At last year's summit, we established the undeniable need for QBL. This year, we will assess the progress made, share initial results, and outline the path forward in transforming Quality from a support function to a strategic Business Partner. The implementation of the six traits of QBL will be a key focus of our discussions.

Key highlights of the upcoming 2025 summit:

- **Regulator Panel led by Professor Kevin O'Donnell, HPRA**

  We are honored to invite Dr. Janet Woodcock, former Acting FDA Commissioner, and other senior level leaders from the FDA, EMA, HPRA, and other national agencies to discuss ongoing efforts in harmonizing the Pharmaceutical Quality Knowledge Management System (PQKMS) and a harmonized regulatory framework.

- **Industry Perspectives on the Transformation to Quality Business Leadership**

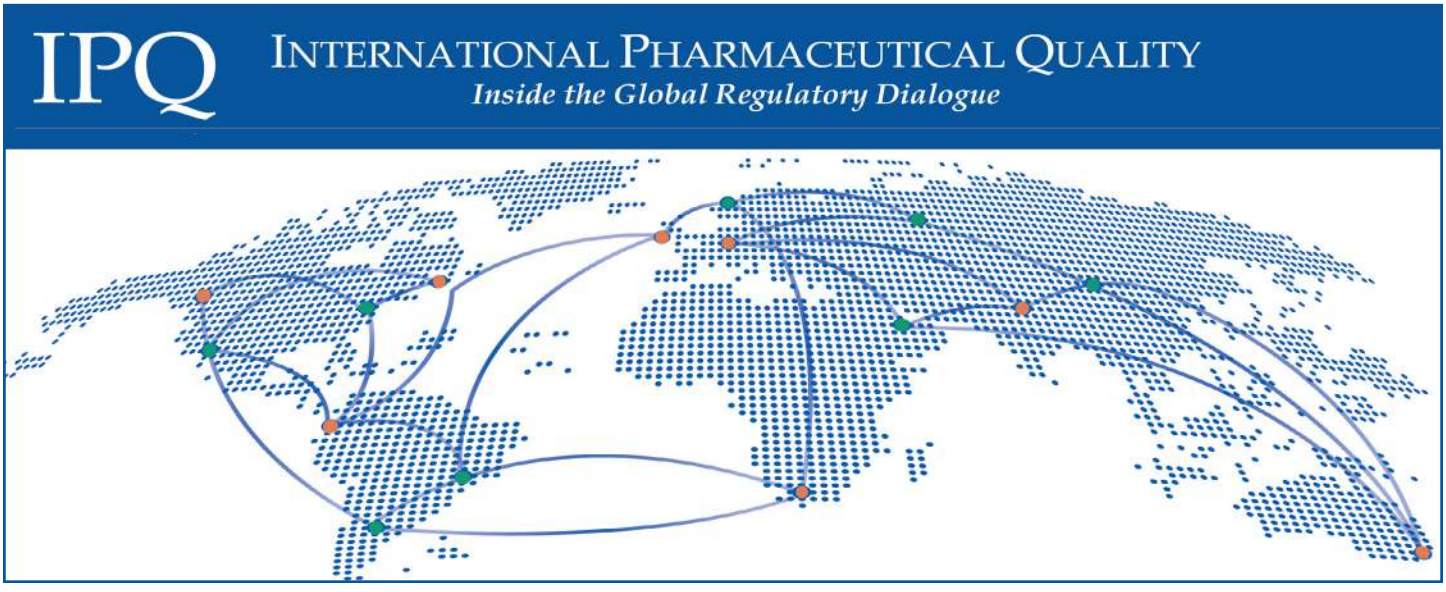
  Industry leaders in Operations and Quality will share strategies and best practices on:

  - Embedding a culture where quality is a shared responsibility across all functions and demonstrated in daily actions
  - Driving engagement at all levels to foster continuous quality improvement
  - Demonstrating quality as a value-driven financial advantage
  - Adapting the Pharmaceutical Quality System (PQS) to integrate emerging technologies, including AI

- **Insights from QBL Program Alumni**

  Graduates from the first cohort of the Certificate in QBL Program will share their experiences, discuss the impact of the program, and highlight how they are embedding QBL into their daily operations with tangible results.

[Woodcock's complete remarks begin on p. 11.]



JANET WOODCOCK ON TAKING A STAND FOR PHARMACEUTICAL QUALITY

At the May 2024 Quality Business Leadership Summit, former FDA Center for Drug Evaluation and Research (CDER) Director and Acting Commissioner Janet Woodcock reflected on her long tenure at the agency, quality challenges over those years, and her hopes for the future. She discussed: ● the history of pharmaceutical quality in the U.S. ● quality at the turn of the 21st Century ● the current state of pharmaceutical quality globally, and ● why quality professionals must take a collective stand to bring needed changes. Click here for the slides accompanying Woodcock's remarks. Formatting changes and other minor edits have been made for clarity by IPQ. Expressions of thanks to the meeting organizer /attendees and disclaimers that the presentation represents the speaker's views and not necessarily those of their former organization are not included.

Good morning. First of all, I would really love to say 'hats off' to Lorraine [Nolan, HPRA] and Theresa [Mullin, FDA], and colleagues.

Does everyone really understand that if this [International Coalition of Medicines Regulatory Authorities (ICMRA) Pharmaceutical Quality Knowledge Management System (PQKMS) initiative is successful, what this will mean?

It won't just mean that we will have a single quality approval. That is kind of the holy grail here. We want to have a single worldwide quality approval so that we have the same product everywhere, and we don't have all this 'stuff.' So I really agree with what Lorraine was saying about reducing complexity. But it is the gateway to a new way of doing things.

I saw on the slide that the assessment from the assessors was, 'It is more work.' It is more work now. But once you start trusting each other and we have that knowledge base and we have the program set up and everything, there will actually be less work for everyone. And of course, we are going to have to tell all the chemists that they are not going to lose their jobs. We will have to repeat that every day during this entire project for the next five years.

But it is such a powerful driver because, as you said, quality is the foundation for everything in pharmaceuticals. And yet, it is universal. So we don't need to have all these regional tweaks and all this stuff.

This project is extremely powerful as a driver of simplification, reducing complexity, and driving change and harmonization. All of this can only help all of us, particularly in the quality area, because it will start exposing some of the issues as we go forward.

History of Pharmaceutical Quality in the US

What I am going to talk about today is somewhat of a step back. It is a little bit historical. I have been, not historical, I have been hysterical for many years about the problems in pharmaceutical manufacturing. [Laughter].

I took some time to learn about how we got to the state we are in – where people make potato chips, automobiles, and everything else with much more automation than we make these valuable commodities. The question is, how did we get here?

This is going to be US-centric because that is what I know the best, but I imagine the story is similar [elsewhere] – although, as was alluded to, Germany, of course, has a long history of manufacturing.

But in the early 20th century in the US, there was no quality. People could put anything into drugs, and there were multiple fatalities. That is how bad quality was. And that actually caused the FDA to start – because of all the quality problems, outbreaks, fatalities and so forth.

Early FDA Poster of Sterile Fill Operation

So, we went along in the century, and I kept a poster in my office until I retired in January. I think it was from the 1940s. It was a sterile fill operation with two women. They were sitting at an apparatus that was filling. They had no gowns, gloves, or masks on, and...one was handing a vial to the other person's bare hand.

There was an FDA inspector in the background wearing a white coat and holding an open vial and inspecting it. And this was a poster. This was supposed to be like the state of the art – wonderful, we are inspecting. So, in other words, we had a long way to go on quality. I just loved that.

Then we had the '62 statutory amendments. There continued...to be a lot of safety problems. In addition to requiring efficacy, [there were] increased safety requirements with early GMPs. I think Europe had a similar trajectory.

GMP Era from the 1970s

Now, then, we had the GMP era that we kind of still have from the 1970s on. I just told you about where we were in the 40s. The 70s were better but focused on quality control and process assurance. That was really what they focused on. They weren't focused on quality management or quality leadership. They were really focused on QC and QA types of things.

The FDA inspectors sought compliance with these requirements. But the fact is that when I came in on the end of this in 1994, when I joined CDER, we were still doing consent decrees. There were many actions and still quality outbreaks going on.

So it took a long time to bring quality up to a minimum floor, which is, I think, what the GMPs contemplated. I started with biologics. The regulation for biologics was more stringent at that time. You had to qualify every facility in a certain way, and you got a license and so forth. They did lot release, which with the biotech then, was pretty funny.

I actually stopped that. I said that if a monoclonal antibody manufacturer cannot do a pyrogen test, then they really shouldn't be in the business. So, when I was at CBER, I stopped doing central lot release for the therapeutics. So that is where we were with the GMPs.

I think my understanding of part of the state of pharmaceutical manufacturing is that it came from pharmacy to a great extent. Of course, the problem with pharmacy and scaling up is that the materials don't scale that well. Many of the problems that we saw back in the days when I started related to those problems in non-uniformity and that kind of thing.

Quality at the Turn of the 21st Century

What happened then at the turn of the 21st century was that the CMC review became increasingly detached from inspections, and I think we are still seeing that.

Right before I left the agency, my sort of swan song was to do an 8,000-person reorganization of the agency, which included changing how our inspectorate works. The goal was to try to bring inspectors back to work with the experts in manufacturing who do the CMC review or assessment, as you all call it here.

When I took over in 1994, the CMC assessors were in each division of FDA, and so the same drug, if it were in psychiatry and endocrine, might have different requirements. I can see some people nodding that they remember this. And this is kind of similar to what we are doing now internationally, where an assessor in Ireland, for example, and an assessor in the US might say, 'Well, we have different levels of this impurity,' or something like that. Then you end up with complexity in different products.

What I did was to form the Office of New Drug Chemistry, which brought all the new drug assessors together. They didn't forgive me for 20 years for that – they were very unhappy. But that really set the stage for our international harmonization, the US part of it, with ICH and so forth, because we obviously could not harmonize if we had all this disorganization.

Our inspectorate at that time was a jack of all trades. They did food, devices, and drugs – even as manufacturing became much more complex and technical. But finally, our field organization reorganized in the early 2000s and became specialists, so we had pharmaceutical inspectors, and so forth.

The agency's compliance function was not fully aligned with either the inspectors or the assessors. I do see some people nodding vigorously in the audience who have experienced some of these problems.

So, I became very aware of this around this time and that is when I said this quote, which obviously failed to achieve that vision, which makes me unhappy.

Industry Perspective

When I talked to the people doing manufacturing in the industry, what they said was, 'Well, we are second class citizens. The goal here is to get those innovative products out the door and make as much money as possible. The message to us is shut up and get the product out the door.'

As we have just heard, quality was not seen as a competitive advantage by the innovator firms [or generic firms]. I talked to generic firms about surely [for] a commodity, that manufacturing would be the thing, but no.

With inspections, I have kind of gone through the evolution here because there were so many enforcement actions over time that were needed – necessary ones. But they were treated as a 'cat and mouse' affair – where can we elude the inspectors and get past that inspection?

At that time, around 2002, I asked a quality leader at one of the major pharma companies and they said, at an open meeting, 'Our quality goal is to pass FDA inspections.' Really? That is your quality goal? But I understand from what people tell me that that is still a quality goal in some cases.

I will tell you that is not a quality goal. For the FDA inspectors, the bar that we set is the floor, below which we would take enforcement action. It does not define high quality. It is not agile, efficient, maximally effective, and so forth. It is what you need to not get a 483, right? And as far as an aspiration or ambition, that is pretty lame.

And so, what happened then – and some of this I am not really sure of because I was not really there and I am not a business person, but I can tell you this is the case – pharmaceutical manufacturing fell behind other industries. The fact that we, at FDA, had to push online sensors – huh? In 2000? – that that would be a good thing to have. That is unfortunate.

Maybe some of it was due to this 'cat and mouse,' this intensive regulatory environment. But I think much of it is what some of you are facing today – that quality is not viewed as a central competitive competency in this business. And that is really unfortunate.

I think that is partly the conversation we need to have today. Because I am not speaking as a regulator now, I am just speaking as a regular person. From everything we know from other industries, it should be a competitive advantage. Quality should be a central part of an industry that produces such valuable products that sustain health and life.

It is very unfortunate I think, this situation we all found ourselves in. That is when I wrote that quote that Anders cited, and yet I think we still have not achieved that state.

FDA Responds with "Pharmaceutical Quality for the 21st Century"

What did we do at that time? We encouraged the modernization of technology, like the use of sensors, continuous manufacturing pilots, and so forth. I got the FDA to join PIC/S [the Pharmaceutical Inspection Cooperation Scheme] and tried to join [up] and harmonize international work on the inspectorates. We started nominating our quality topics to ICH to build a foundation of internationally harmonized standards.

And we began efforts to stress quality culture and quality management as an overall objective rather than FDA being the QA department in the sky. And I think there was a culture –_I can't speak for other regulatory agencies, but I think for FDA – it was like we should be their QA department.

But no – we are a government agency. That is not our job. So, there were some unfortunate mutual interactions I think that helped lead to this state. And the field staff, the inspectors at FDA, were not fully aligned with the center staff. So the reorganization I just completed before I left will hopefully remedy that situation. But industry is often not getting a single message from the regulator. That is a real problem.

FDA is still working, as many of you well know, on quality metrics – on how to measure and incentivize quality culture. Because that is something that is much more difficult to get your arms around than 'Do you have an SOP, and have you validated this and that, and so forth?'

But basically, I think it isn't the regulatory agency's responsibility, and a regulatory agency can't make a quality culture in a company. That is the responsibility of the people in the companies.

Current State of Pharmaceutical Quality Globally

So, what do I think the current state, the global state, of pharmaceutical quality is?

- Well, as Lorraine already said, we continue to see serious lapses in quality, not just in the emerging manufacturing hubs, like India or something – we certainly see them there – but within the US and Europe. This causes industry to take multiple reputational hits.

  And I would say in the United States with the discussions that are going on about pharmaceutical pricing and everything, this is a very bad thing. And so, the CEOs of your firms may want to take some notice of this, because every time the industry takes a reputational hit, your standing in a negotiation diminishes.
- Generally quality production of these extremely valuable products that you make is not at the level attained by many other industries. In other words, when you talk about six sigma or something, that is not what we are talking about here.
- Quality professionals are still not seen as major corporate players in many of the companies, and that is a huge problem, I think.
- High-quality manufacturing is still not understood or believed to be a competitive advantage.
- Of course, regulators are generally on board with and supportive of firms' strong quality culture, and there has been much more understanding of that.

However, the companies say to us, 'Well, if we do this, what will you give us?' As I say, it really should not be the regulator's responsibility. Sure, it would be great if we could figure out ways to measure and then incentivize very high quality. But really, that is part of the problem – saying it is somebody else's problem. It is really the company's problem. It is their responsibility.

Everything tells us in business that you have to own quality yourself. You can't have somebody else force it upon you. This is the current state, in my mind, despite decades of effort by various individuals, including me.

What is Needed to Effect Change?

What is needed to change this situation? As I say, change has to come from within the industry. The regulator's role is to encourage, not inhibit – but we cannot require this. It is over and above that floor.

Individuals advocating within companies have not effected the needed change. And I don't know enough about that because, over the last several years, I have been involved in other stuff, so I haven't been talking to my confidential informants about what is going on.

I think a new strategy is required because it has been over 21 years since 2002 and we still are not there yet. I really suggest a united and collective effort by the discipline would be the right thing to do. In other words, the discipline of quality professionals in this industry.

The data on the value of quality are available. This isn't some mystery. Other industries have figured this out. Everybody knows this business value to quality.

Society: Overall, you are going to have a lot of advocates on your side. Society does not like the idea that quality is not very important to the people making these valuable products.

Currently, pharmaceutical quality has a poor reputation. Of course, that is because any time there is a quality breach or whatever that is in the news, blah, blah, blah, and they talk about it, and so forth.

So, there is a real reputational hit here. And I am very aware that I have taken a rap with the U.S. Congress, as we all have to, and they think about these things. These are very important political arenas.

The Need for Quality Professionals to Take a Collective Stand

I think the quality professionals, the people in this room, and others need to take a collective stand, which is why I called this 'Take a stand for quality.'

- Develop common objectives and principles and publicize them. Own this. Don't look to the regulators. It is not the regulator's responsibility.
- Highlight the data on the business value of quality and the need to reverse the current societal perceptions and reputational hits the industry is taking because of the quality breaches that we see.
- Collectively and publicly advocate for appropriate placement of quality leads within the corporate structure. I know you can't go and do this to your own CEO and say, 'I should have a higher job.' But if, collectively, it is said that, you know, this is how, say, you are supposed to treat a CIO [Chief Information Officer] in the government.

  When I was acting Commissioner, I found out our CIO was very down in the organization, which created horrible problems. I pulled that person up, empowered that organization, and rapid change happened. So, I think it is important to create an expectation that the quality professional will have a very high ranking within the company.
- Train quality professionals in corporate leadership on the business side. It is not just about making sure you are applying what have you. It is really business leadership you are going to be talking about, I think.
- And finally, develop realistic options for regulatory incentives. You know the regulators are not going to do this for you. I think one of the central principles of quality is it has to be owned by the people who are doing the work. And that is not the regulators.

Now is the Time for Collective Action

So that is my own advice here. I think now is the time to take collective action for a variety of reasons – not just this project that Lorraine and Theresa Mullin are doing, this fabulous opportunity.

I think company leadership is pretty focused on reputational woes right now, especially with the price negotiations going on in the United States.

Regulators worldwide have reached the point where they are going to be very supportive. The cost of the quality problems has never been more evident. With all the shortages that are going on, the public is really talking about this.

Individual within-firm advocacy can only go so far. It is not like you alone are going to be able to forge something. Some people may – some powerful personalities or a conjunction of circumstances – but in general, I think united [efforts in] creating that expectation is the way to go.

And a visionary, united approach can change expectations and achieve results. Of course, who am I to say so after 20 years? I haven't achieved the results, but keep trying.

Summary Comments

In summary, pharmaceutical quality has a long and rather notorious history. The last few decades have seen many advances, I will acknowledge that, but there are continuing quality lapses, and those are the ones that make the news, not the good stuff.

Quality needs to be recognized as an essential business capability and a competitive advantage for firms. That is why, in my quote, I had 'agile and flexible' – agile because we are going to have shortages, and we need to be able to move on a dime. We need to be able to react to circumstances like the pandemic.

Quality leaders need to have appropriate status in corporate hierarchies, or you are never going to get this job done.

And united action by the pharmaceutical quality leadership is needed to take this to the next level. Thank you very much.

[O'Donnell's complete remarks begin on p. 17.]

International Pharmaceutical Quality

ABOUT IPQ's WEEKLY SUPPLEMENT

Along with a feature story on a presentation or panel discussion at a recent conference in which leading regulators address the challenges and developments in a key area of concern, our Weekly Supplements include a summary listing of the "Updates in Brief," drug GMP warning letters and recalls, and EMA non-compliance reports that have been posted on IPQ's website during the week. Subscribers can then click through to the full posting.

Appended are the headlines of: ● the "regulator insight" stories featured in our Weekly Supplements since IPQ began publishing them in January 2024, and ● the in-depth stories that IPQ has released since 2020. Those of especially high relevance are indicated with a red star. Click on the headlines to access the stories.

HPRA'S KEVIN O'DONNELL ON QUALITY LEADERSHIP AND THE ROLE OF ICH Q9(R1)

At the Quality Business Leadership Summit in Dublin in early May, HPRA Market Compliance Manager and Rapporteur for ICH Q9(R1) Kevin O'Donnell gave a presentation on the role of ICH risk management guideline in quality leadership. He discussed: ● what good quality leadership is ● the current focus on pharmaceutical quality system (PQS) effectiveness ● a case study on effective PQS in a global biologics company ● risk-based change management ● a case study on a poor QMS at a CMO, and ● the relationship between quality leadership and PQS effectiveness. Click here for the slides accompanying O'Donnell's remarks. Formatting changes and other minor edits have been made for clarity by IPQ. Expressions of thanks to the meeting organizer / attendees and disclaimers that the presentation represents the speaker's views and not necessarily those of their former organization are not included.

My talk is about quality leadership in the context of the ICH quality risk management guideline Q9(R1). The guideline was revised in January last year after a few years of very hard work by a very big team. So I would like to show you my thoughts regarding how the revised guideline can help quality leaders achieve their objectives.

Good Quality Leadership

What is quality leadership? I asked a few colleagues and friends: 'What does good quality leadership mean?' Some people said: 'It drives innovation and productivity and culture.' We heard from one person – an inspector from Austria, actually – who said: 'It is when you don't need more than one attempt to implement projects.' Another person said: 'It is about knowing I can make mistakes and I won't lose my job or be disciplined.' Others said it was about motivation and productivity, having effective work, the retention of staff, and ideas, innovation, efficiency and results.

For me, in the context of working in a manufacturing site making medicines, good quality leadership should ultimately result in an effective pharmaceutical quality system (PQS). I feel that is a thing we should be striving for.

Quotes from the European GMPs

This concept of an effective PQS is supported by the GMPs. Within the European GMPs, there is the requirement that 'manufacturers must not place patients at risk.' And Dr. Woodcock mentioned earlier that manufacturers have placed patients at risk due to significant quality lapses.

So it is the objective of senior management to try to do this – not to put patients at risk. The GMPs speak about having a 'correctly implemented PQS,' where its effectiveness is monitored. That is what I want to focus on today – PQS effectiveness, which includes appropriate quality risk management, which Lorraine mentioned earlier, and how senior management does have responsibilities to ensure that an effective PQS is in place.

And the last nice quote from the EU GMPs, in Chapter One, is about leadership: 'Senior management leadership and their participation in the PQS is essential.' The new guidance and Q9(R1) is actually a pretty good framework I think to help quality leaders achieve this PQS effectiveness objective.

Current Focus on PQS Effectiveness

But why speak about PQS effectiveness now? Is this a new concept? Well, ICH Q12 highlighted it as a significant core requirement of accessing the Q12 flexibilities, so some might think it came in with Q12.

Q12 speaks about an effective PQS being necessary to implement that guideline, especially in relation to change management. It says, 'an effective change management program will support the principles of this guideline.'

But PQS effectiveness is not a new concept. It has been in the GMPs for decades. And really, as inspectors, we are trying to get a handle on how effective a company's PQS is when we are doing our inspections. And ICH Q10 actually highlighted it really nicely too.

Q10 has appendix 1, which is not very much spoken about actually, but which I think is really powerful. It speaks about opportunities open to companies if they do certain things. If they demonstrate – and I think Lorraine used the word 'demonstrate' in her talk this morning – that an effective PQS is in place, and if they apply the concepts and principles of Q8, Q9, and Q10, there should be opportunities open to them.

The lower bottom right of the table in the ICH Q10 annex refers to 'optimised science and risk-based post-approval changes,' which is what Q12 is mainly about. Conversely, if companies just comply with the GMPs – and actually just looking through number 1 and number 2 in the table and the others, those things are part of the GMPs – but if companies just comply with the GMPs from a very minimalist perspective, they should not expect to get regulatory relief or flexibilities from regulators.

Remember this Appendix in ICH Q10?

- **Potential Opportunities to Enhance Science and Risk Based Regulatory Approches**

Scenario	Potential Opportunity
1. Comply with GMPs	Compliance – status quo
2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g., ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk based approaches for regulatory inspections.
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).	Opportunity to: • facilitate science based pharmaceutical quality assessment; • enable innovative approaches to process validation; • establish real-time release mechanisms.
4. Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk based approaches for regulatory inspections; • facilitate science based pharmaceutical quality assessment; • optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement; • enable innovative approaches to process validation; • establish real-time release mechanisms.

ICH Q12 Opportunities

So, the opportunities are there, and regulators have put mechanisms in place for the industry to gain such opportunities. But we rarely see companies come and ask for them. We know that the industry wants ICH Q12, and it wants the regulatory flexibilities that it offers, but individual companies don't seem to come to us very often to say, 'Listen, we have a really good quality system at our site, and we want to come and talk to you about maybe getting some regulatory relief in this area or in that area' – maybe starting small and moving on to bigger opportunities. We don't see companies come and discuss such things with us.

In relation to granting regulatory relief, it is important for regulators to be careful, and not to be reckless. Recklessness, I think, was a word in Holger [Rathgeber's] slides. Regulators have to be a little conservative regarding how we do things. We cannot just be handing out regulatory flexibilities where they are not warranted.

So, it is important for companies to demonstrate that an effective PQS is in place when they come looking for such regulatory relief. Dr. Woodcock made the point this morning that it is not up to regulators to fix the problems of manufacturing and the challenges in the supply of medicines. It really is up to the industry. And the tools are in place for this, and Q9(R1) in particular can help in this area. The revised guideline refers to PQS effectiveness in a few places, and here are a few of those quotes ***[see slide #10]***. The last one there is, 'an effective PQS drives both supply chain robustness and sustainable GMP compliance.'

Drug shortages are relevant to mention here, as they are very often linked with the lack of those things – supply chain robustness and sustainable GMP compliance. Some companies that run into significant GMP non-compliance have to stop product release, and this sometimes does impact upon the supply of medicines, leading to patient impact. And one of the reasons why Q9 was revised was to try to address this very area – manufacturing and quality issues giving rise to increased risks of drug shortages.

We know there are many other reasons for drug shortages, and the Q9 revision was only focused on the issues referred to above. ICH Q9(R1) speaks about the importance of 'early warning systems' – that wording was put in there specifically in relation to product availability risks – and the importance of having good oversight, using knowledge management and quality risk management, to address evolving issues.

ICH Q9(R1) and Quality Leadership

But what does ICH Q9(R1) have to do with quality leadership, which is the topic of today's seminar?

ICH Q9(R1) refers to these six things here. Apart from maybe risk-based decision-making, none of these things, at least for me, really links easily to quality leadership. But, for me, all six are related to quality leadership, and I want to show you two case studies that illustrate how these things really can help quality leaders ensure the effectiveness of their PQS.

The first case study is about a biologics company, quite a big site in Ireland, that is focused on continual improvement and ICH Q12. Case study two is very different. It is about a small contract packaging site, a CMO, struggling with non-compliance issues and with a recent incident in their quality control lab.

But What Does ICH Q9(R1) Have To Do With Quality Leadership?

The 6 revision topics addressed in ICH Q9(R1) and in its accompanying training materials of October 2023 are the following:

- *Subjectivity in QRM*
- *Product Availability Risks*
- *Formality in QRM*
- *Risk-based Decision-making*
- *Risk Review*
- *Hazard Identification*

Let's consider two very different **case studies** that show the relevance of this guidance in relation to Quality Leadership & PQS Effectiveness

Case Study 1 – An Effective PQS in a Global Biologics Company

This case study concerns a large site that manufactures monoclonal antibodies and other biologics products here in Ireland. It has had a good compliance history, with no major deficiencies cited over the last 10-plus years. The site has also had a strong focus on continual improvement. We saw evidence of this during all recent GMP inspections.

Their parent company wants to access a number of ICH Q12 flexibilities. Those flexibilities relate to one of the drug products manufactured and released by the Irish site. The parent company wants to register – and Lorraine mentioned this this morning – post-approval change management protocols [PACMPs] that relate to a number of areas relevant to the Irish site's product.

So, where does the site's quality leadership fit into this ICH Q12 world?

I know we have a lot of quality leaders here this morning, and some of you may work at drug product manufacturing sites. The staff and the head of quality at the Irish site have had little exposure to Q12 up until now. The company's CMC regulatory group are the ones that know the most about handling marketing authorization variations and ICH Q12-related submissions. They are located in the US and the UK, but not in Ireland.

Role of the Local Manufacturing Site in Relation to ICH Q12

So, the question is, does the Irish site have much of a role, if at all, in seeking these Q12 flexibilities? And what would be the role of the site's quality leadership in this area?

From my perspective, the site's quality leaders actually have a vital role because, while they may not know the ins and outs of the Q12 regulatory framework for getting variation applications involving PACMPs written up and submitted, they do have expertise in two areas that are absolutely pivotal for Q12 – PQS effectiveness and change management.

Plus, the site has done a lot of work to improve its quality risk management competencies over many years, so it is well-placed to feed into the regulatory submissions that will seek, and make the case for, those flexibilities, as Q12 refers to operational flexibility and how it is contingent upon the application of QRM. So, those things will be important.

GMPs – PQS Effectiveness, QRM and Change Management

We have the GMPs, which speak about PQS effectiveness, quality risk management and change management, and, as mentioned in one of my earlier slides, they require 'a comprehensively designed and correctly implemented PQS' to be in place, 'which is effective.' And the GMPs assign the 'ultimate responsibility' in this area to the site's 'senior management.'

There is also an annex to the European GMPs called Annex 15, on qualification and validation. It refers to change control, and how change control is important to link with quality risk management and knowledge management.

So, if I were with this company in Ireland, whose parent company wants it to seek certain regulatory flexibilities, as a quality leader, I would focus on demonstrating to the regulatory inspectors and others the effectiveness of my PQS, especially in relation to risk-based change management.

PQS Effectiveness, QRM & Change Management in the EU GMPs

- The EU GMPs emphasise the importance of PQS effectiveness, QRM and risk-based Change Management
- Remember these quotes from Chapter 1, *Pharmaceutical Quality System:*
  - '... there must be a **comprehensively designed and correctly implemented PQS** incorporating GMP and QRM…. it should be fully documented and its **effectiveness monitored'.**
  - **'Senior management** has the ultimate responsibility to ensure an **effective PQS** is in place…"
- And in relation to Change Management, Annex 15 states:
  - 'The **control of change** is an important part of knowledge management and should be handled within the pharmaceutical quality system.'
  - **'Quality risk management should be used to evaluate planned changes…** and to plan for any necessary process validation, verification or requalification efforts.'

ICH Q9(R1) provides a very practical framework for this. Remember how earlier I mentioned the six key topic areas that were the focus of the Q9 revision? One of them was **formality in QRM**.

The new guidance in this area refers to understanding the level of uncertainty, importance, and complexity in the QRM activity or area being risk-assessed. For me, this is directly relevant to change control because in change control: ● there will be some uncertainty, given that the proposed change will be happening in the future ● there may be a degree of importance associated with the proposed change, and ● there may be high levels of complexity as well.

So, for quality leaders reviewing change control proposals, it can be useful for them to review the proposals in the context of the extent of QRM formality that is required to support the change control, and the above three concepts – uncertainty, importance and complexity – provide a framework for doing that.

Risk-Based Change Management

Hazard ID is also one of the six areas of concern in the ICH Q9 revision. This area is also relevant to Q12 flexibilities, because in change control – and we see this quite a lot – making changes can introduce hazards that will need to be identified, risk-assessed and managed. And additionally, other hazards can come into place when implementing changes that may also have been unforeseen.

Some of you in the room this morning are from a company in Ireland that presented at a conference on the topic of change control in 2012. One of the company's Irish sites was experiencing issues with serious deviations and recurring serious deviations, and a Six Sigma project was initiated to gain a detailed understanding of the problem and to find solutions.

And guess what? While the company went into the project thinking that the problem lay with the management of deviations at the site, the project revealed that the problem actually lay with the change control process at the site. It showed that 28% of all serious deviations were directly related to previous change controls, whereby hazards had been introduced during the implementation of those change controls and had gone undetected. That was a very interesting learning for that site.

Another company here today also experienced a significant change control problem – and in that case, a very severe drug shortage was the result, significantly impacting patient treatments for several years. That case related to the implementation of what had been classified as a like-for-like change at a CMO that the company used to manufacture the product.

The CMO site was replacing a seal on the door of a dryer that was used in a sterile API process. They replaced the seal with one they thought was an equivalent seal. But guess what? The new seal was not equivalent, it had subtle differences, and it did not maintain the sterile barrier when the dryer was operating.

The next aseptic process simulation that was run on the process failed, and after a long investigation, the failure was traced back to the loss of dryer integrity, and that issue was found to be directly related to the use of the improper seal on the dryer door. Production of the medicine in question ceased at the CMO for several months, while the investigation into the issue progressed, and by the time the issue got resolved, there were no manufacturing slots available at the CMO to manufacture new batches of the product.

The result was a supply problem with a very important medicine that lasted for several years. Change control can indeed be challenging from a hazard identification perspective.

Subjectivity in QRM outputs

Let's now look at subjectivity in QRM outputs. This was another of the ICH Q9 revision topics, and again, it is relevant to ICH Q12 and to this case study, because risk assessments are often needed to support change control proposals, and there can be subjectivity in those assessments, such as in the ratings that are arrived at for risks. The goal, however, is to have objective risk assessments that lead to evidence-based GMP controls that support the implementation of changes.

There are many things we can do to try to reduce subjectivity, such as addressing the influences of cognitive biases. And there are other simpler things we can do too: One is to ensure that all risk ratings are supported by GMP controls. So, before we write down a probability rating, it is important to first consider what preventative controls are in the process for the hazard or risk in question, and to not only document those controls in the risk assessment, but also to consider and document their likely effectiveness.

The same goes for detection controls. We see a lot of 'high detectability' ratings in risk assessments, where detection ratings of 'one' indicate a very high level of detectability, but often there are no detection controls that support those ratings. And when detection controls are present, sometimes they are not likely to be effective for the specific hazard or risk in question, for various reasons.

So the likely effectiveness of risk controls is important to consider in risk assessment but so also are the qualification and validation requirements for those controls. Often, the qualification or validation requirements for GMP controls that help keep risks low – or green – are never assessed.

I have to say I personally have never seen a risk assessment tool out there that addresses the above points, but I think they make sense, and they are not too far out there to think about implementing them. These things, I think, will result in less subjective risk-based decisions in relation to change controls.

And actually, should change controls be expected to result in reduced risk? Reduced risk could come in the form of reduced process variability, a lower likelihood of defects, reduced product availability risks, higher levels of supply chain robustness, etc. Why wouldn't these be the expected outcomes of effective risk-based change management activities? And if a company is striving towards continuous improvement, should its change management activities not serve to reduce risk? I would hope so. I would like to hear your thoughts on this.

Looking Forward with Risk Review

Risk review, one of the other six topics addressed in the ICH Q9 revision, is also relevant in the context of ICH Q12 and this case study. ICH Q12 refers to 'having no unintended consequences' as a result of a change, and risk review is useful here as a look-back exercise.

But for me, risk review is not just about looking backward – for example, we did a risk assessment six months ago, and now we are going to review it. It is also about looking forward, and this is very relevant to change control, which is about looking forward.

Highly effective change control activities address the following question: 'What post-change monitoring will we be doing after we implement the change to make sure the change is going correctly for us?' This is an important thing to consider. The new training material on the ICH website for risk review refers to this very thing.

Product Availability Risks

Lastly, let's consider product availability risks. We have been speaking about drug shortages a little bit this morning. At the HPRA, we see many serious quality defects every year that have arisen from change controls that have gone wrong for companies, and those can result in the cessation of batch production.

Last month I was in a company and this very thing was happening. They had made what looked like a fairly minor change to a packaging process, and by the time I got there, they had stopped production and the release of two different products that were packaged on that line because of serious quality defects occurring in the packaged products that related to that simple packaging process change. The supply of these two important products was jeopardised by this product availability risk.

So, it is important for quality leaders to assure themselves that any new hazards and risks that may be introduced during change control activities are identified and managed. If they don't, suddenly they can find themselves in a drug shortage situation.

But drug shortage risks are not just related to product quality issues. Regulatory compliance issues are also important to consider, as these can also lead to the cessation of production and batch release. And in an ICH Q12 world, the potential for this is probably heightened, as there are now more things that can trip manufacturing sites up in relation to regulatory compliance, such as the need to comply with Post-approval Change Management Protocols (PACMPs), and Product Lifecycle Management submissions (PLCMs).

QPs have to think about those things, and they have to assure themselves that the batch they are certifying is in compliance with any PACMPs and PLCMs that are in place, as well as with the more standard aspects of the marketing authorization, and of course with GMP.

So, regulatory compliance becomes more complex, I think, in an ICH Q12 world.

PIC/S Paper on PQS Effectiveness and Risk-Based Decision-Making

Lastly, for this case study about PQS effectiveness and quality leadership, there is a PIC/S paper from July 2021 that is useful to consider. The paper is titled 'How to Evaluate and Demonstrate the Effectiveness of the Pharmaceutical Quality System with regard to Risk-based Change Management.' It contains a tool that sites can use to demonstrate to their regulatory inspectors the effectiveness of their PQS in relation to risk-based change management.

I would like to mention two people who were important in the development of that PIC/S paper: Dr. Emma Ramnarine, who is not here today, and Dr. Anders Vinther, who is here. Emma works with Boehringer Ingelheim, and together with Anders, she contributed ideas and content when PIC/S was developing the paper, and this was invaluable. Both of them actually worked a lot with Dr. Wookcock in the past, in relation to post-approval change management and the One Voice of Quality initiative. Those colleagues were very helpful to us in PIC/S when writing this PIC/S PQS effectiveness paper.

Actually, when writing the PIC/S paper, regulators put our money where our mouth is by stating in the paper that if a company implements the guidance that the paper provides, that will serve as sufficient evidence that an effective PQS is in place with regard to risk-based change management. That was a strong statement and an important one to have in there.

So, we hope that companies will use that PIC/S PQS effectiveness paper. When it comes to inspections, companies could, for example, invite their GMP inspectors to review their change management process against the guidance in the PIC/S paper, in an effort to demonstrate the effectiveness of their PQS in that area. Lorraine mentioned ICMRA this morning, and Dr. Woodcock also referred to it. I mentioned this here because ICMRA has identified the PIC/S PQS Effectiveness paper as being important in supporting its PQKMS (Pharmaceutical Quality Knowledge Management System) initiative.

So, this brings us to the end of Case Study 1. I hope it has illustrated for you how ICH Q9(R1) provides a **ready-made framework** that quality leaders can use to demonstrate the effectiveness of their PQS in relation to risk-based change management and ICH Q12.

Quality Leaders can also make use of the PIC/S Paper on PQS Effectiveness

'How to Evaluate and Demonstrate the Effectiveness of the Pharmaceutical Quality System with regard to Risk-based Change Management', July 2021

- The paper contains a tool (checklist) that Quality Leaders can use in relation to their change management activities.
- Its guidance is useful in supporting the implementation of ICH Q12, "where **mature risk-based change management** within an effective PQS is considered foundational to enable greater regulatory flexibility in reporting of post-approval changes."
- Application by a manufacturer of the PIC/S guidance **"will provide evidence of the effectiveness of their PQS** in relation to risk-based change management", where "maturity in change management may support… the regulatory flexibilities discussed in ICH Q12."

ICMRA has cited the PIC/S paper as an important tool in facilitating its ongoing PQKMS initiative.

Case Study on a Poor PQS at a CMO

I will be very brief with this case study. This is about a CMO at the other end of the spectrum – not a big multinational company, but a relatively small contract manufacturer that is struggling with a poor history of compliance and a recent QC incident.

The site in question performs primary and secondary packaging of non-sterile products. They have had a poor compliance history, with major deficiencies [non-compliances] identified at each inspection for the last number of years. In June of last year, there was an incident whereby a QC analyst had assigned an approved status to a bulk batch of prednisolone 5mg tablets after its receipt at the site for packaging, without doing any of the required QC tests or checks on that batch.

The issue went undetected until the QC manager spotted it randomly a few weeks later, on July 10, 2023, and he notified the head of quality about it. We were inspecting the site 11 days later, on July 21, 2023, and we came across a deviation that referred to the QC issue. We asked about it, and we were given a deviation report that had been raised the previous day.

Serious PQS Failings

Within probably half an hour of reviewing the deviation, we realized that there were very significant PQS failings at this site. And they were not just about QC.

By the time of our inspection at the site, the QC approval that had been given to the batch by QC had still not been withdrawn. There was no second-person review process in place for any QC results and checks, the company had done no checks of any other batches that the QC analyst had recently checked to determine if he had done the same thing with those batches or if it was just one batch that was impacted, and the deviation had only been raised 10 days after the incident had come to light. This was all unacceptable, given the seriousness of the issue.

We reviewed various other records, including those for a batch of methotrexate 10mg tablets that had been assigned a QC approval status by the same analyst. We noted that the appearance specification for that product was 'round, white tablets with a scoreline,' but the tablets were round white tablets with no scoreline.

One might not think that is important, but with methotrexate, we have two strengths of tablets on the market, 2.5mg and 10mg, and every year there are serious adverse reactions reported for patients who have had their methotrexate medicine mixed up, where the 10mg strength is taken instead of the 2.5mg strength. Such incidents can be very serious, and some have resulted in fatalities. So a QC check of tablet appearance is critical.

We also reviewed the training that had been provided to the QC analysts at the site. We found that no practical on-the-job training had been given to the analyst in question. My friend Jim Vesper, who is here today and who is a world expert on QRM, often refers to how 'read and understand' training is better described as 'read and hope' training. This company just gave that analyst 'read and understand' training during his first few days in his role, and he had no prior experience in QC or in any capacity in pharma before taking up that role.

We then moved to the warehouse where we reviewed a number of goods-in records. There were no goods-in records in place for the checks that were required to have been made on the batch of prednisolone 5mg tablets when it had been received at the site. This was also a major PQS failure.

Lack of Quality Leadership and Application of Q9(R1)

Looking at this case from a quality leadership perspective, what are its messages? Well, for me, their handling of the case was very poor from a leadership perspective. Their actions did not reflect the seriousness of the issue, and many fundamental GMP controls had failed – not just in QC, but in materials management in the warehouse, in training, and in deviation management. The result was that very serious GMP non-compliances occurred and risks to patients went unmitigated.

Looking at this case through the lens of quality risk management, I believe that the new guidance in ICH Q9(R1) could have helped those senior leaders deal with this issue better, had they applied it. For example, a little while ago we spoke about the concept of **formality in quality risk management**.

In this case here, the company didn't apply an appropriate level of formality when assessing the risks presented by this QC incident. Remember earlier I discussed how the concept of formality in ICH Q9(R1) is about three main things: ● uncertainty ● importance, and ● complexity.

In this case, the company's actions did not reflect the importance of the issue – the lack of QC testing/checking of a batch before its QC approval. They also didn't realise the importance of immediately quarantining the batch when the issue came to light, and no such quarantine had been applied. Their actions also didn't reflect the degree of uncertainty that was present. It was not actually known whether the batch had been received from the approved supplier or if it even was prednisolone tablets.

In relation to **hazard identification**, another of the ICH Q9 revision topics, no attempt had been made to identify other hazards that may have been present in light of this incident with prednisolone tablets. The company had not worked to identify whether any other batches were treated in the same way as the prednisolone batch.

For me, unchecked batches in a warehouse or in a manufacturing plant with a green QC approval sticker on them can be thought of as a hazard. The company also didn't review the training that had been given to the analyst. For me, poorly trained QC analysts can also be considered a hazard, especially when those people are in a position to approve materials with no oversight applied to their work.

Risk review and **subjectivity**, two of the other topics in the ICH Q9 revision, were also overlooked by the company when dealing with this case. This incident with the batch of prednisolone tablets should have triggered them to look back at a risk assessment that had been done the previous year, in 2022, when the company had risk-assessed its QC activities. That risk assessment had been in response to major deficiencies that the HPRA had identified in the site's QC activities in 2022.

They didn't do any such risk review, but when we reviewed that 2022 risk assessment in light of this prednisolone deviation, it was clear that all risks had been assigned a low-risk rating on the basis of QC staff training. The company had concluded that its QC function was operating correctly because its staff were well trained. This prednisolone case told us that this wasn't the case.

In relation to **subjectivity**, it was clear that those risk ratings in the 2022 risk assessment were highly subjective, as there was little objective evidence that the QC staff had been properly trained. Risk review could potentially have helped the site detect this issue also, had they done a risk review of that 2022 risk assessment.

Risk-based decision-making was another of the ICH Q9 revision topics, and the new guidance on it could have helped in this case also. As is evident from the above, very poor decisions were made by the quality leadership at the site in relation to the QC issue, and the decisions that were made were not sufficiently risk-based. We have a colleague in the room here today, Valerie Mulholland, who is about to complete a PhD on the very topic of risk-based decision-making. I look forward to reading your research findings Valerie, and learning from them. Good luck.

The ICH Q9(R1) guidance on risk-based decision-making refers to three approaches to such decision-making: ● highly structured ● less structured, and ● rule-based. The guidance on rule-based decision-making would probably have been the most applicable to the QC leaders at the site when dealing with the prednisolone QC issue.

That guidance discusses how in rule-based decision-making there are SOPs, policies, or well-understood requirements in place, which determine what decisions must be made. Here, there are rules, or limits, which govern such decisions that might be based on a previous understanding of the relevant risks and usually a predetermined action.

In this case, the quality leadership could have made the following decisions: ● one, immediately quarantine the prednisolone 5mg tablet batch ● two, withdraw its QC approval ● three, open a deviation and work on it with urgency ● four, remove the analyst from any further QC work until the issues and risks had been resolved, and ● five, immediately put in place a second-person review of all QC data and reports. But they didn't do any of those things.

So, the **key takeaway messages** from this case study are that poor-quality leadership can result in an ineffective PQS, and patients can be put at risk. ICH Q9(R1) provides leaders with a framework to not only manage specific deviation issues but also, more holistically, to manage the pharmaceutical quality system so as to get it to a place where it can be deemed effective.

Quality Leadership and PQS Effectiveness Relationship

This brings us to my last slide. Quality leadership, to me, goes hand in hand with PQS effectiveness. They are interrelated concepts. An effective PQS should ultimately be a direct output of good quality leadership. I use the word 'ultimately' here because if you are a new quality leader who goes into a site with significant problems, you might not have an effective PQS right then. But ultimately, over time, we would hope that, with good quality leadership, that can be achieved.

The Q9(R1) guidance provides a framework for achieving an effective PQS, and not only when things are going well, as in case study 1, but when things are terrible, as in case study 2. The revised guideline also provides quality leaders with a framework to demonstrate the effectiveness of their PQS to GMP inspectors and others.

But – and I was reminded by what Dr. Woodcock said earlier – there are a lot of people involved in making these things happen, and quality leaders should not feel that they are on their own in striving for an effective PQS. There are many people at manufacturing sites who contribute to the effectiveness, or the ineffectiveness, of the PQS.

[The full QBL morning panel discussion begins on p. 28.]

QUALITY BUSINESS LEADERSHIP SUMMIT PANEL DISCUSSION

Participating in a panel discussion at the morning session of the QBL Summit were: Ireland Health Products Regulatory Authority (HPRA) CEO Lorraine Nolan, former FDA Center for Drug Evaluation and Research (CDER) Director Janet Woodcock, HPRA Compliance Manager and ICH Q9 (R1) Rapporteur Kevin O'Donnell, and industry consultant Holger Rathgeber. Joining the morning speakers on the panel was EMA Scientific Officer, Brendan Cuddy, who is Chair of the Inspectors Working Party (IWP) The moderator for the discussion was Quality Business Administration (QBA) Founder and CEO Anders Vinther. Topics covered included: ● a cautionary tale regarding learning from the airline industry ● the financial advantage of quality ● the relationship between culture and change, and ● the concepts of "coopetition" and "cultural assassins." Minor edits have been made for clarity by IPQ

Cautionary Tale of Learning from the Airline Industry

Paul Adams (NIBRT): Dr. Woodcock got me thinking there when she mentioned other industries being ahead of pharma, such as the airline industry with six sigma and the way they have been working. Boeing has had some recent problems with the [US government]. So I am wondering, are there some lessons learned from that incident?

And if we are thinking about – and sorry for putting words in people's mouths here – maybe regulators should be less hands-on? They should not be the QA department. Let the companies do their own quality. But with that, I think we have seen the problems with Boeing, where maybe too much was given over to them. So, are there lessons learned there, and are there any comments about quality leadership? How do we avoid something like that happening in our industry?

Janet Woodcock (Former FDA): Well, I think with Boeing, the message is internal vigilance for reputational decline. And that is what has happened. Although I flew over here from the US, and I can say that a lot of people are concerned about flying right now. Boeing is in trouble with the US government. They are in trouble with the airlines because of having been quarantined.

It is very similar to what we have just talked about. And my approach has often been misunderstood. I am not saying that the regulator should not oversee the industry. There will always be people like Case 2 [a case study presented by O'Donnell], who are just completely problematic.

But really, quality needs to be owned. And I think what happened with Boeing is that they were not owning that quality, and people were doing things they should not do. Because they were failing to put bolts back on or whatever they were doing. As we know, quality has to start with the shop floor and go all the way through.

So, I just feel that to get to this next level industry really needs to take the lead themselves. The reputational loss we saw with Boeing and the resulting vulnerability of Boeing are the results of their own lapses in vigilance. And I mentioned all this because I think this is a business case you take to the management. Because, as I said, I feel this has all been neglected by the senior management of companies, and there is a cautionary tale there. Boeing is a great tale.

Kevin O'Donnell (HPRA): I don't know the ins and outs of the Boeing case, but senior management responsibility cannot be stressed here enough. The aviation industry has done a lot of risk assessment work over many decades.

Many airlines have a very good safety history, but there are some who don't. I think it is important to realize that lapses can occur even within very good companies, for various reasons, through complacency, for example, or as a result of poorly managed changes, or whatever.

So really, the role of senior management in monitoring the effectiveness of the PQS is really important, because an effective PQS is needed to prevent or detect such issues, before they result in disaster.

Lorraine Nolan (HPRA): Thanks very much, and I am not going to comment either on the Boeing case. It is not my area of expertise. But I would concur with what Janet and Kevin have said in terms of reputation and the use of risk management principles in terms of the aeronautical and also the automobile industry, and even, of course, the food industry.

So, I think one of the things I have often thought about that can inform us – and it speaks a little to what Kevin said – when you look at maybe the stagnation in the application of quality risk management principles, and very much the methodologies that have been used over decades but are not really advancing. I am just wondering if pharma is a little bit too insular in terms of how it approaches risk management and doesn't look outside of its own sector enough….

Brendan Cuddy (EMA): My background is that I have dealt a lot with incidents and crises over the years. So from a regulator's point of view, I guess it is important that there is really good communication between the industry and the regulator at the time of an incident so that it doesn't become a crisis.

For us, that is really important that we get the information as quickly as we can about whatever the issue is that we are dealing with – so that we understand what you know about it and what you don't know about it. That will allow us to ensure that we have an effective regulatory response at the end of the day.

Ultimately, we have to make a decision to protect public health, and we need to have the best information in order to do that, which isn't always easy. But that is our objective really, and that is our role – to ensure that we safeguard public health.

Anders Vinther (QBA, moderator): So we are also worried about reputation – that was talked about in a few of the presentations as well – and what do we do as quality business leaders? During the break, I was talking to a couple of you and one of the things we talked was 'there is a lot of common sense here, so why is it we are talking about the same things…after 20 years?'

Financial Advantage of Quality

Barry Heavey (Accenture): Lorraine, I was really intrigued and excited to hear you talk about the effort to create the 'super-body' for post-approval changes, especially for some of the big modalities that are mainstream now, like mAbs and ADCs.

I am just wondering: One of the core traits is the ability to talk about the value of the financial advantage of quality. We talked a lot about the value of agility, but it is hard to quantify sometimes the value of agility.

Does the industry perhaps need to do a better job of trying to put a quantification of the financial value of being able to bring in these valuable changes in manufacturing for these new modalities of continuous manufacturing, PAT, and show really how much true value will be brought into the supply chain – maybe even a hypothetical molecule or something, not to talk about specific molecules, but maybe a hypothetical one.

Woodcock: I have had some opinions about that. Thank you for raising that issue. I think one of the disadvantages of this industry is, for a very long time, it has treated every aspect of the industry as competitive. And everything was buried in secrecy. And so, your toxicology is all secret, and your lab work and development is individual. You can't do that because you can't develop an individual biomarker, right, because it won't be widely accepted, right? I mean, that is the definition.

But the toxicologists in the companies got over this about 20 years ago when they started pooling and sharing the data. The biomarker developers are working in collaboration, sort of a consortium, to try to pool data and develop biomarkers of common use. Even the basic science people are working together now and collaborating.

This industry really competes on its molecules, not on all of this other stuff. But manufacturing – and this is really a pet peeve of mine – where is the scholarly base for this? Where is the study of pharmaceutical manufacturing and scholarly input? We got the National Science Foundation in the US to support a couple of academic centers for continuous manufacturing and training of pharmaceutical manufacturing personnel.

So, to get to your point, I really believe that manufacturing and quality is not a competitor type of thing. I really think you ought to unite.

The real-world examples we heard are hair raising. In example two, it could have killed people with that. And most companies will not have that degree of problem, we hope. But I think you are talking about the positive aspects, so sharing the advantages. What happened when we switched to better processes? How many defects did we prevent? How many batches no longer got thrown away? So, reduced waste and better efficiency.

These things, I think, aren't shared to the extent they could be. And they could make a very powerful case for a widespread improvement in the overall quality in industry. So, part of what I think ought to be done is really get over the fact that it is not a competitive thing, manufacturing. It is a shared technological activity.

Quality management is also important. If you pooled the data and had some venue where you could do that, you might be better able to convince your very senior managers and CEOs that that investment is really a sound investment.

Nolan: I have very little more to add to that… I suppose selling the value proposition within companies is a bit of a general answer. It depends on what you are trying to solve. I mean, when you go back to the PQKMS [Pharmaceutical Quality Knowledge Management System] project that I set out earlier, I know we are leading it with FDA, but it really is a team effort. And I am sorry Brendan, because I didn't properly acknowledge the huge role the EMA has had in that project as well.

You know, when you look at that model, and you saw the slide in terms of the different way of managing post-approval changes, on the face of it you would say, 'Okay that has to be less costly, fewer submissions, fewer processes.' But actually, the real value add was demonstrated during the pandemic where we had to rapidly scale up vaccine manufacture, and there was enough stock produced to almost vaccinate the world population.

So, the value proposition will hugely change depending upon the scenario. I think there is a huge opportunity here in terms of addressing the problem of shortages because, as Kevin has pointed out, all too often, there are multifactorial manufacturing issues – and changes in manufacturing actually tend to be one of the really big contributory factors in medicines shortages.

If we had a better way to address this, it could really help. It could really make a difference. And again, that plays into selling the idea of less reputational damage for companies, because the prevalence of drug shortages is really, really increasing. The media coverage of shortages is really increasing. We are seeing that in Ireland, and I think there is a huge reputational risk for all stakeholders involved.

I also agree with all of the points about commercial sensitivities and sharing among the industry. It is something we see all the time. But I think in this area, there are huge opportunities for quality where more can be done.

Cuddy: Just a couple of remarks to add to that – hopefully, a slightly different perspective maybe. But if you ask patients what they expect from you, they are your customers. They are who you are trying to satisfy and gain your competitive advantage with. What do they want from you? They want medicines that are like electricity. They turn the switch, and their medicines are there. So that is your goal.

Your objective is to ensure a continuous supply of medicines. So, you need to think: okay, agile, flexible, excellent, really good – but also resilience. You need to be able to withstand shocks. If you have agile within supply chains or within production and you have an issue, how do you bounce back after that?

Can you get back into production really fast? Can you overcome that problem? So, it is really important to think about supply chain resilience as well. And a key feature, I think, of supply chain resilience is your people.

We talked about management and quality leadership, of course. But there is a very important sentence in Chapter 2 of the GMP guide, the very first line: 'The correct manufacture of medicines relies on people.'

If you are going to gain a competitive advantage, if you are going to ensure a continuous supply of medicines, you have to understand your people. They are making daily decisions about quality. They are monitoring the process, adapting to the process, and they are learning from each other. And that learning, as we can see from Kevin's case study 2, is not linked to your training program.

So, the learnings are from each other. You need to understand that and incorporate that into your risk assessment. From my point of view, this is a really important thing that the EMA, together with the network, has been talking about for over ten years – the need to introduce these proactive risk assessments to enhance your supply chain resilience and ensure the continuous supply of medicines for patients.

Nolan: Thank you very much, Brendan. I am just mindful of a point I really wanted to make from the beginning here today. Inevitably, the issue of shortages was going to come up.

It is very challenging. And all of us would say these last two years in relation to managing shortages have been [challenging] to all of us. But at the end of the day, one of the issues we have in terms of shortages is that the contributory factors are multi-factorial. The number of stakeholders involved is many. And there is almost a suggestion that nobody owns this.

But at the end of the day, it is the pharmaceutical manufacturing industry that actually makes the medicines available for the market. So, the ownership piece is the thing that really has to come first. Time and effort are what is needed to go into this. And even when you take it back and look at the practicalities of demand and supply, oddly, that is where we see things often go so wrong in that that is just not done optimally.

And I know that may not necessarily be a quality function, and it may not be perceived in that way, because that is a much more commercial activity. But in terms of patients and how that links to quality, we can't disjoin those functions within an industry or organization and make them silos. They all have to come together to get the right outcome for patients as well too. So, I think we need a bit of a reality check on where is the ownership of this actually coming from.

Vinther: All right, those were a lot of good comments there and some take-home messages – the electricity supply and the ownership of the industry in terms of drug shortages and avoiding that, and the quality business leadership we are discussing today.

What we will come back to this afternoon is one of the big challenges we, as quality leaders, have: When we ask for something that prevents an issue from happening, that is a budget item. And we have to fight much harder for that than when we have to then say, 'Oh, it happened.' So now it goes on the P&L [profit & loss] – and that is usually at least 10 times more expensive, right?

Another topic mentioned is competition versus collaboration. Janet and I have talked quite a lot about this. We really would like you, as a quality community, to think about quality business leadership as not a company thing, and it is not a competition thing. It is better for everyone if we have really competent quality business leaders. It really is.

One of the things Holger and I have talked about, which I think is very interesting, is he mentioned the experiment with the monkeys, which was a real experiment, but also culture is a little bit like we play a certain type of music on the radio and the person who has decided on the station may have long gone from the company. But we still play the same music until someone asks, 'Why are we playing the same music? What would we like to listen to?' Does anyone have a question for Holger on engagement and culture?

Relationship Between Culture and Change

John O'Sullivan (Eliquent): One of the questions I have is regarding the common principles, which I know that you are actively involved with, and creating a burning platform. You talked a lot in your presentation about culture. So, do you believe that culture needs to be right to create the impetus for change, or can change occur in the absence of that culture that you described?

Holger Rathgeber (Consultant): That burning platform was one of those ideas that Prof. John Kotter put out very early in his career and he regretted it later. Because it really took root. The metaphor is pretty bad if you think about it. If you are on a burning platform and the only choice you have is to be grilled or to jump 100 meters into ice-cold water, that setting is not creating the right set of behaviors. People become quite dysfunctional if you put them on a burning platform.

The point is, and the better way to think about it, is how do we create a *burning desire*?

In my presentation I pointed to an insight of Barry Johnson. His key insight: It is human nature to think in terms of good and bad, right and wrong. So, when we feel there is something wrong, we attack it from a position of 'I am right.' But this 'wrongness' very often actually exists because someone pursues something else with good intent. And what we attack is just the shadow side of something good being driven very hard, too hard.

You can never engage a person in a constructive conversation about how we can balance those tensions between trust and control, between collaboration and focus, between procedures and experimentation if you attack them on the shadow side of what they actually intend to do. That was a big insight I had from Barry Johnson and his book on polarities.

The work that we have done in driving cultural change in the vaccine company I used for my presentation – the consulting firm was Kotter – was very much guided by four core principles:

- First, if you want to make people do something that requires courage, it is not a pure intellectual exercise. You have to really touch them in a sense emotionally. It is not just head, it is a lot about the heart.

- Second, you have to get beyond those select few and tap into the diverse many. All too often people really think they are tapping into a large percentage of people to do continuous improvement or even cultural change.

This will not stand a fact-based assessment. It is total fantasy. You have projects and initiatives, but if you do the math, it is less than two or three percent of employees that are actually doing it, while the implied message to the rest of the organization is basically: 'Keep doing what you do unless you are told otherwise.' That is not tapping into the diverse many.

● Third, to activate the diverse many, orders and the chain of command are not effective. You have to tap into the want-to versus relying on the have-to.

● And realistically, the fourth principle is probably the biggest one: It has to do with not just managing, but we also need a high enough dose of leadership. Leadership is giving direction, giving hope, giving purpose, and allowing people to come together to do something that no one else can do alone – ultimately, lead the path, inspire action, and remove barriers for people to do something at all levels.

Because stuff will get in their way, and it always will, you will need the big guys and girls to knock down barriers that frustrate people and stop them from moving. So, leadership from the top is always an integral part, yet it is by far not sufficient. You need leadership from many seats.

Finally, you need to dial up urgency, particularly in the beginning. It is not a burning platform, but a burning desire. You must find creative ways to move this desire or ambition into the window of attention of people that is labeled: 'Very important. Act now.' And let me tell you, this window is small, and lots of people fight over it. You must do something bold to get into that window for a large enough number of people to get momentum.

I have probably answered five more questions that you didn't even ask.

"Coopetition" and "Cultural Assassins"

Vinther: So, I was thinking that there are lots of pains. I was thinking about when you ask people, "Would you like change? Everybody raises their hands. Then when you say, 'Will you change?' fewer people raise their hands.

When you ask the next question or make a statement, what are your thoughts on this transition from quality leadership to quality business leadership?

Nuala Calnan (PRST, TUD and QRM consultant): Just a few remarks on the last item there to reinforce it. There is this concept…that emerged in 2021 after the pandemic, called 'coopetition.' It is competition through cooperation and collaboration. And that is what we need to do. It says where it works best is where the parties coming to cooperate do not have any fear of their secret sauce – their molecule – being at risk. But they have a great opportunity to create value for their business by coming together.

I agree with you, Dr. Woodcock. What we see here today, with TU Dublin hosting this thought leadership, is that more scholarly work on this is needed. We are happy to take on that mantle and create this space where these studies, discussions, and cooperation – or coopetition – can happen.

The last thing, just to Holger's point, another book that I picked up last week talks about the importance of having 'cultural architects' in your organizations who are building the culture. Having spent the last 10 years since my own PhD in this area of quality culture doing just that, they also warn about the 'cultural assassins' that you meet along the way.

And that is what I see. I see people, even quality leaders, who are desperately within their organizations trying to build the infrastructure around cultural architecture, to put that in place with behaviors and leadership. But very often, coming behind them, back to the plane metaphor, they are building the plane and flying the plane, and someone is dismantling the plane behind them – where we have these hierarchies and silos where people are protecting their patch.

Yesterday we had a wonderful day with the St. Gallen team as a 'warm-up' event…and we talked about the fact that, with these cultural assassins, they can be literally undermining the whole effort that is going ahead – irrespective of the fact that you have leaders who are desperately trying to shine the light and lead the way through their own behaviors. So, we have to acknowledge those and call them out, and be able to name that and own it as well.

Vinther: Are there comments on Nuala's [remarks] about cooperation and about the cultural assassins?

Woodcock: I certainly would have comments about that. In all the change efforts I have done, I have certainly encountered, you might say 'really ingrained resistance.' And what I have concluded is: just think about the people, whoever they are, and why they are doing it.

It might partly be for maintaining control and prestige, and there is a lot of that. But a lot of people simply don't see things the way you see them. And your job is to talk them into it. My change effort went like this: talk, talk, talk – and persistence – persist, persist, persist.

Because we keep saying that people resist change, but they don't really resist change. They resist your framework of the problem. And if you can get them to shift to understand the problem the way you understand the problem, then all of a sudden, they are on your side. But that takes time for people to talk, talk, talk – a great deal. And a lot of people who do this assassination [do it] because they feel they are losing control.

So, you have got to try to figure out how they can feel comfortable, maintain control or whatever, and still go along with the change. Some of them don't and they are going to have to go. But people can come along, and you have to figure out where they just don't see it the way you see it.

Holger: Cultural assassins or 'no-no's' – those people getting against you, which actually is a good sign if they show up. It means you are starting to get serious. They recognize you and they do not ignore you. The little hint here is two-fold: It is a really bad idea that I have seen as a practice: 'Oh, we wrote this [with no one in].'' So it becomes kind of. 'We will convert them.' Ninety percent, that doesn't work. It slows the team down to make progress.

Second, there is a tendency to spend way too much energy on these 'no-no's,' particularly at the beginning. Your job as a leader is to make the early adopters win. So, the numbers outside will get siloed, more and more siloed, the more you make those people actually on your side successful.

And thirdly, if they are in a powerful position, knock them down as soon as you can, because they will create a huge shadow over their own organization that will ultimately undermine your credibility as a leader if you allow them a place. So that is not a friendly note. But if you are serious, you have to consider it.

Nolan: This is just a very small point, I suppose, reflecting on this as we are talking about change management. Across all organizations, it doesn't matter what area you work in, it is the same. It is all about people, and it is all about getting people through change.

A number of years ago, in our organization, we made the decision to bring the change management programs in-house. We do use consultancy support sometimes, but we do a lot of the work ourselves. I have to say, that really was a game-changer. It did mean we had to grow some more, and I absolutely echo what Janet has said: 'talk, talk, talk.'

Sometimes, you feel like Moses wandering around in the wilderness with the amount of talking, but actually it is such a big investment because you get the buy-in from people, and you actually get the gain later on.

The other part I would say is to always treat people with value. Most people are nervous about change because they actually feel 'what does this mean for me?' and are no longer valued. It really is convincing people that you still value them, there is still a place for them, and it is about growth and a change in mindset.

Final Comments from Panelists

Vinther: Does anyone have anything relating to this session you would like to share in the last 30 seconds?

O'Donnell: I guess regulatory risk is a difficult area to get right, so working together to get really world-class risk assessment tools in place – and we can use them as regulators, as much as you could use them as industry. So, [my final comments] would be to increase the standards of the tools we are currently using.

Nolan: I would say the importance of the role of the relationship between regulators and the industry…. I think there has been a mindset change in the project I spoke about. The future and the success of that is actually about working together to co-design, and it is a wonderful opportunity if we can highlight and embrace it.

Cuddy: I am not going to say much other than to thank all of the speakers who spoke so eloquently today and answered lots of questions. Can I just say that it is a huge honor to be on a panel with Lorraine, Janet, and Professor Kevin. It was absolutely fabulous, so thank you very much.

[Vinther's complete remarks begin on p. 36.]

QBA'S ANDERS VINTHER ON SPEAKING CGMP AND $GMP

At the Quality Business Leadership Summit in Dublin in early May, Quality Business Administration CEO Anders Vinther discussed the importance of being able to speak about good manufacturing practices from the perspective of both current requirements (CGMP) and financial terms. He discussed: ● what good quality business leadership is ● how quality as a value requires speaking a new language ● the relationship between ICH Q10, quality risk management (QRM) and financial risk score, and ● operational excellence. Click here for the slides accompanying Vinther's remarks. Formatting changes and other minor edits have been made for clarity by IPQ. Expressions of thanks to the meeting organizer /attendees and disclaimers that the presentation represents the speaker's views and not necessarily those of their former organization are not included.

I will speak from the perspective of my experience. For six years I was reporting to the Chairman of the Board of the company that I co-founded. He is a venture capital executive. This is a quality guy reporting to a venture capital guy, so I learned a lot about articulating why we need quality.

The presentation was actually made in collaboration with two people: ● Craig Elliott, who I worked with at Genentech. Then he became the CFO [Chief Financial Officer] of PDA, the Parenteral Drug Association. He was there for a few years and then moved on to do something else. And then ● Carmen Kerschbaum, who previously was the senior vice president at Pfizer in their finance department.

What is Good Quality Business Leadership?

'Promote quality as a value-driven financial advantage:' That is one of the six traits for quality business leaders. You see all six traits in Figure 1.

The 6 Quality Business Leadership Traits

All right, so we will start with this picture ***[slide #3]***. On the left side, you have a quarterpounder with cheese and on the right side, you have the grilled lamb riblets from Restaurant Evvia. The title is 'quality you can taste.'

And thinking of quality you can taste, so the one on the right is the one you take your family out to, and you can talk about a week in advance and so on – let's go and have a really nice meal. And you are okay that it is going to cost more than a quarterpounder when you get the bill because you can see it and taste it and feel it. You have that overall feeling about the quality that is just really good.

Quality in Drug Products

Now, with drug products, you can't really taste or feel or see the quality. You just expect it to be there. And it is not that I can think, if I am a patient, I would like a really, really good quality pill – not just a pill. We don't even talk about that, right? No, here is the pill and we just expect that it is good quality and the supply is uninterrupted. So that is what we expect – quality.

So therefore, I say for quality for pharmaceuticals, we really only experience it when it is not there. We experience it when it is not available – when we have drug shortages. We experience it when we have adverse events. It can be hyper or hypo-potent. You can have safety events, or it might not be efficacious.

So that is when you know that the quality is not where it needs to be, but you can't really see it. And then there are all the things that Janet [Woodcock] talked about earlier today – about let's not set the bar at the minimum here. As a company, we might have lost batches, received 483s, or other regulatory observations that cost money to do something about. Warning letters also show quality at a level below where we need to have it.

Both of these have **reputational damage** for the company. And actually, the one on the left can also have financial damage because you don't sell what you want to sell when there are drug shortages. People might start asking where this product comes from. Which company is it from?

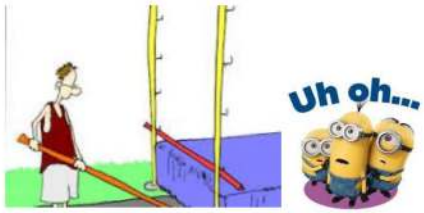
Minimum Compliance or Quality Business Leadership?

So I think it can be hard for a quality professional to go to the CEO or to the finance leaders and say we want to spend more money in this area, and the finance guy might say, 'No, that is enough money for quality and compliance this year.' I have experienced it more times than I can remember that somebody has said, 'Where in the regulations does it say we cannot cut this corner?'

So then, okay, where do we want to go here? Are we going to go with minimum compliance or are we going to go with what we now call quality business leadership?

'Better' Quality Can Be a Hard Sell Within Company

Minimum Compliance



- Leaves you in risk of non-compliance with cGMPs
- Quality seen as a cost
- Reactive quality leadership
- Historically, compliance has been the focus for Quality

Limitation of Quality role

Quality Business Leadership

- Set bar at 'the right place'
- Use PQS as engine for quality, technological, & financial improvements
- **Quality Business Leaders demonstrate value of quality in words, actions & results**
- Focus on fit for purpose
- Demonstrate business acumen

Expansion of Quality role

The difference between them really is that if you are on the side of minimum compliance and set the bar at the lowest possible level, you are constantly facing the risk of non-compliance. You always have the risk that it is not really where the bar is, it is a little bit higher than that.

'Minimum compliance' companies usually see quality as a cost that they want to reduce as much as possible to achieve short-term cost savings. And you end up spending all your time dealing with issues, and it is actually a very symptomatic indication of the 'minimum compliance' company.

We had about three or four more senior quality leaders that were going to come today. But in the last couple of days, they said, 'Sorry, but I can't really be there. I have to deal with an issue.' So that is what we do, many of us, also in the big companies. We end up being reactive, dealing with the issue of the day instead of focusing on the longer-term strategy to get us to quality business leadership.

Where should the bar on the right side be? Should it be here, here, here, or here? We have got to make sure it makes sense so that we can achieve sustainable product quality, supply, and financial performance – all at the same time.

What I think we have not been good enough at generally in our community of quality leaders is to use the quality system as that engine that drives not only quality improvements but also financial improvements. Because when you do both, then it is a 'no-brainer.' Improved quality leads to better financial performance.

So, what we want to do is to demonstrate the value of quality and not the cost of quality. And we will come to how you do that.

Quality as a Value Requires Speaking a New Language

These two birds don't really understand what the other one is saying. One is the CFO, and the other is the CQO. So one is talking cGMP, and the other is talking dollar or euro GMP.

Objective for all is to continuously ***improve quality, progress technologies, & improve*** company ***profitability***
& uninterrupted supply of quality medicine to patients

And sometimes we just talk past each other. 'I said I just told you. I just told you what I meant.' 'Yeah, but I didn't understand you. If you can't speak euros with me….' I mean, that is the language of the C-suite, right? If you can't speak euros or dollars or yen, it is very hard to understand. Not because the Finance and Executive leaders don't want to, but because that is not the language they have.

I remember sometimes people would come to the senior executive, saying, 'Oh man, that 211.194 so and so, we are in violation of that.' And the executive would say, 'Okay, and what does that mean?' So you need to be able to speak their language.

Translating to $GMP

So if we translate from cGMP, how do we do that so that the finance people understand it in their language, $GMP? What we want to do is to translate from CGMP into three financial concepts: ● one is related to revenue ● one is related to the cost of goods, and ● one is related to labor costs.

And then when you speak to the finance people, they will understand that. And don't forget that quality comes first. But we need to speak both quality and financial terminology.

It doesn't always have to be the CFO we need to communicate with. Find somebody who is influential in finance and make that person your best friend and make sure that he or she understands compliance and quality terms also. But be good at translating it. That is really what you want.

Where the Money Goes

This is a Cost of Quality model. Jane [Wyatt, Alexion] had something like that as well. This one is kind of a modified Juran cost-of-quality model.

What I am saying is that many companies actually do not necessarily know where the money goes when it comes to quality. So it is difficult to say, 'I am going to make some improvements here' when you don't know where the money goes. You should be saying, 'I want to have less recurrent deviations. I want to do this. I want to do that' – and think both quality and financial improvements.

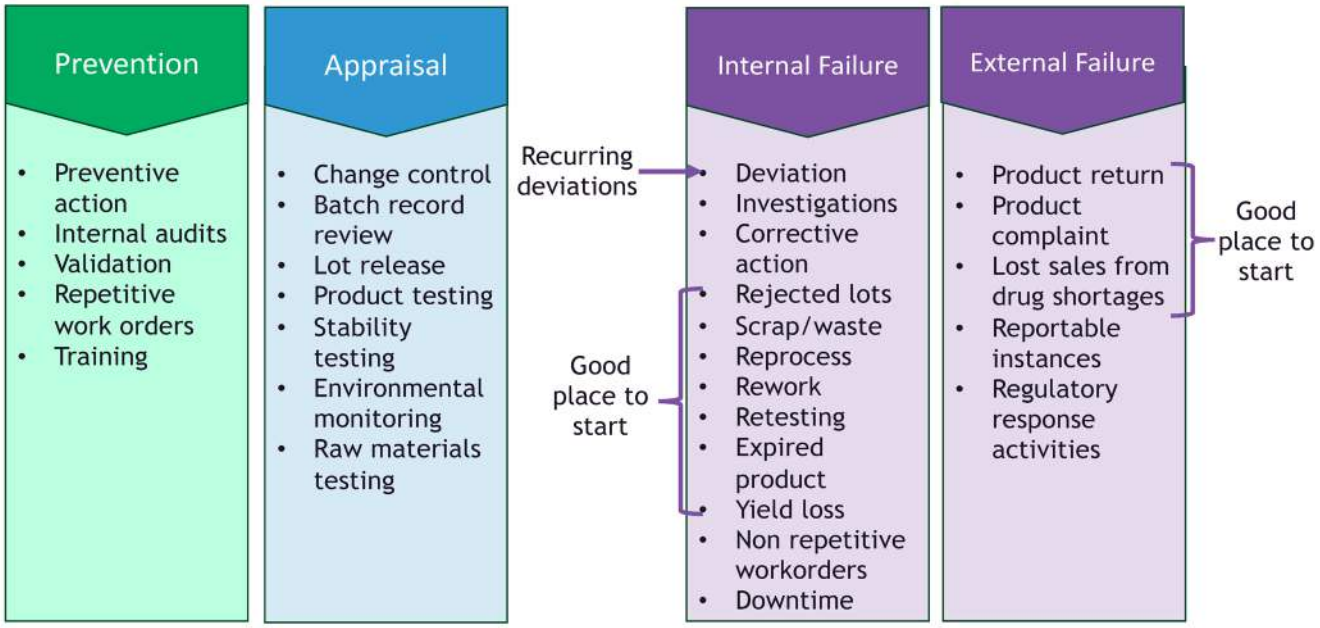
I will start with the cost of quality elements that are a good place to start. It is easy to get numbers on rejected lots, reprocessing, retesting, and so on. You can put a number on that. And if you start looking at how much is that, I see companies that say, 'Oh, that is about, let's say, 4%.'

So if you have 3.8%, then 'Yeah, I meet the budget, right?' But that really should not be the goal. The goal should be zero percent. You should always strive for driving that down and avoiding rejected batches, even though it is in the budget.

And then I think the deviations is an important one. Figure out how we need to do that. See how much we actually spend on deviation handling, particularly those that are recurring.

Where the Money Goes

You can't improve if you don't know where the money goes



Where the Money Goes, From Another Angle

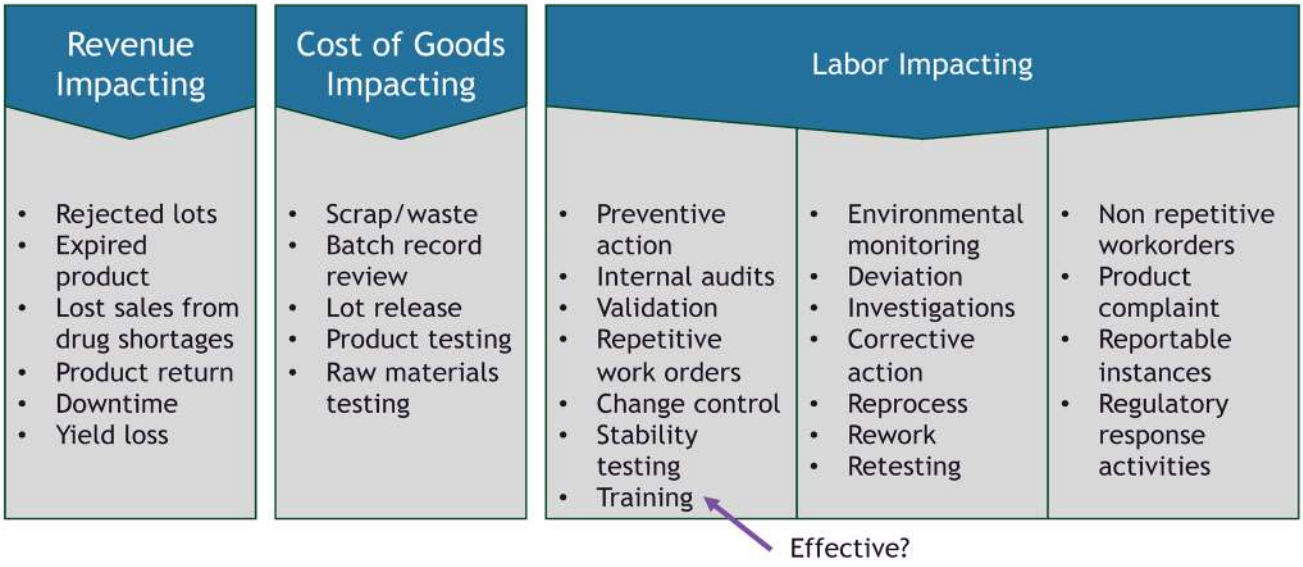
If we take the next slide, then these are the same boxes, and the same categories, but now it is easier for a finance person to understand it. And maybe also for us, in quality. So I have taken all of them and said, 'Okay, some have revenue impact, some have cost of goods impact, and some are labor impacting.'

For the labor impacting costs, it is really about moving from correction to prevention. So the money that you had in the budget, make sure that it goes to prevention and not only to correction. That is really what we want to do. So I think that is very important that we start doing that.

Where the Money Goes, From Another Angle

Many activities are labor driven

Shift focus and resources **from correction to prevention**



ICH Q10, QRM, and Financial Risk Score

I came into a meeting with my CEO, and I said, 'Here is the risk register.' And he said, 'Alright. I see you have got severity, occurrence, and detectability and you have got your RPN [risk priority number] score. And you have got a long list of risks on the risk register. And I can see your ranking but how am I supposed to prioritize?' So we didn't have a good conversation.

I said, 'Alright, give me a week and I will come back.' So when I went back the next week, for every risk, I wrote what it would cost to prevent it from happening and what it would cost to fix. These were not exact numbers, but ballpark.

And then I said, 'In addition to the RPN score, I also have an FRS, a financial risk score. So that is the correction cost over prevention cost times recurrence.' All of a sudden, we had a fantastic conversation. And we increased the budget for the following year significantly because the CEO could see, 'Oh my gosh, there is a high likelihood that these things are going to happen, and if they happen, they are really going to be expensive.'

So if there is a 50% chance that this is going to happen and cost us $10 million, then maybe we should avoid that from happening. So, the FRS is really good for when you speak to finance.

ICH Q10, KM and Institutionalizing Knowledge

When I think of the two enablers in Q10, we worked a lot with quality risk management. Kevin [O'Donnell, HPRA] talked about the role of the quality system. I think, in general, we are not very good at actively enabling knowledge management.

One of the things that we have is something HR calls the 'employee attrition' – you might call it something else, but it is basically the percentage of people leaving in a year or a month, and you trend that.

But there is a big difference if it is a person who has been there 15 years and one who has been there 15 months in terms of knowledge, right?

Use of ICH Q10 Enabler QRM: Financial Risk Score

Correction Cost is Usually Much Higher Than Prevention Cost

- ***Prevention*** cost: known, *planned*, budgeted expense (reduce probability of failure)
- ***Correction*** cost: *unplanned* P&L item (the failure happened), can cause unanticipated changes to revenue and profit

Compliance Risk Score: $RPN = S \times O \times D$ — Severity (S) Occurrence (O) Detectability (D)

Financial Risk Score: $FRS = \frac{C}{P} \times O$ — Cost of Prevention (P) Cost of Correction (C)

Decisions should be made based on RPN **&** FRS

Generally, we expect that the one who has been there 15 years knows a lot more and has a lot more knowledge that he or she leaves with than the one who has been in the company 15 months. How do you make sure that companies institutionalize knowledge, and how do you make sure that these people do not take all that knowledge with them?

So, that is what I have been writing about here.

Use of ICH Q10 Enabler KM: Institutionalize Knowledge

Loss of Knowledge Through Attrition is Costly

Knowledge retention by

- Institutionalizing in the PQS (lessons learned, knowledge reports, APQRs, etc.)
- Extracting knowledge from outsourced operations
- Reducing attrition (thus avoiding 'relearning')

Employee Attrition: $EA = \frac{L}{T}$ — Number of employees leaving (L) Total number of employees (T)

Knowledge Attrition: $KA = \frac{L}{T} \times Y$ — Length of service for people leaving (Y)

You want to think about lessons learned, you want to take those lessons learned and put that into the quality system and so on.

You also want to extract knowledge from **outsourced operations**. When you outsource a lot, all of a sudden, all of your knowledge is sitting in your CDMO. So, you might own the product, but you might not know a whole lot about the process. How do you make sure that you know the process as well?

These are the things you ought to have as part of a knowledge management plan. And that also ties into the financials because it is expensive to hire new people and train them. It is really expensive. So, from a financial perspective, that is something we need to think about as well.

Opportunities in the PQS

Here are some opportunities in the quality system. On the left side are the three objectives of Q10: ● achieve product realization ● establish and maintain a state of control, and ● facilitate continual improvement.

Opportunities in the PQS

ICH Q10 Objectives	Financial Opportunities in the PQS, Examples
Achieve Product Realization	• Reduce risk of drug shortage (drug shortage prevention plan) • Enhance process capability & robustness • Advance technologies & AI
Establish & Maintain a State of Control	• Reduce recurring deviations, get to root cause • Reduce waste caused by compliance issues • Eliminate risk of non-compliance
Facilitate Continual Improvement	• Constantly work on reducing PQS complexity, simplify processes • Make change control system catalyst for change • Use PQS for knowledge growth, learning & retention

Effective Management Reviews:
Set PQS objectives to improve both quality & financial performance

And here are some of the things that I think we as quality leaders should think about. We need to have a drug shortage prevention plan – not only from a supply perspective, which is very important, but also from a financial perspective. It is costly not being able to supply, to stock out.

Of course, you want to make sure you don't throw a lot of product away because it is not meeting your requirements. So process capability and robustness will prevent that. Implement new technologies.

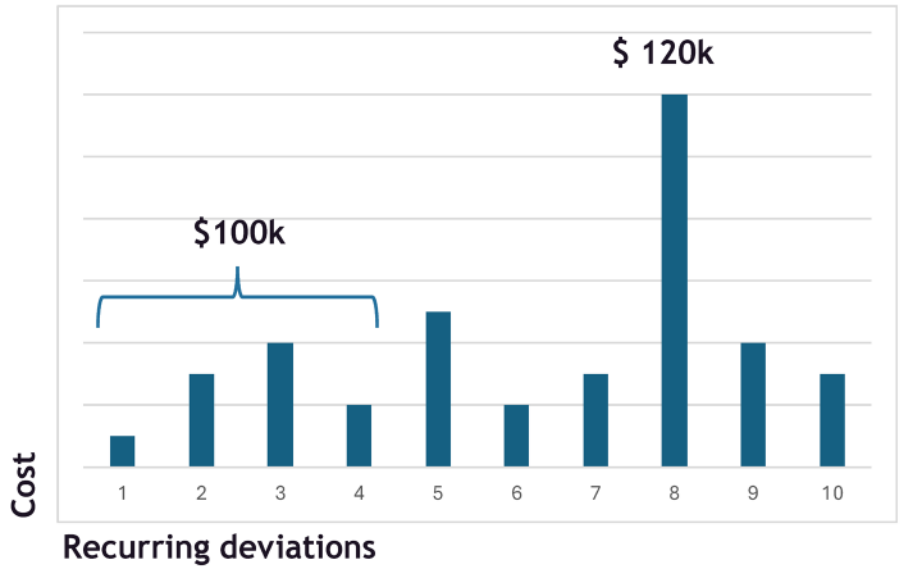
And then on the control side, reduce recurrent deviations, get to the root cause, and then make sure that everything else that relates to non-compliance really should not happen. Non-compliance, in general, should not happen.

One thing I am big on is reducing the complexity of the quality system, which I think is so badly needed. Every time we do something, it usually adds to it. One of the things that Holger [Rathgeber] mentioned, one of the examples, was that they reduced the complexity by 65% on the site, and it was incredible how much more efficient they were. Also, people actually wanted to do the changes. Before, it was just, 'Oh no, I am not going to do it. It is just too complicated.'

Addressing Deviations

Here is an interesting example. These are 10 recurring deviations, every one of them costs what you can see there. So, the first four: if I reduce or eliminate those, I will save $100k. I would then take four out of ten recurring deviations out, reducing my recurring deviations by 40% and saving $100k. Or I could just take that number 8. So now I reduce recurring deviations by 10% and save $120k.

Opportunities in the PQS, Continued



What's best?

Eliminate 4 recurring deviations or saving $120k

By a show of hands, who would go for the four? Who would go for the number 8, to save $120k? It looks like a 50/50 split. But you would never go for the number 8 if you didn't know that this is the one that costs a lot of money, right?

If you just see them as a list of recurring deviations, you would just say that addressing four is much better than one. Why did you only do one when you could have done four? These are conversations that are interesting.

Operational Excellence

The next one is operational excellence. So Lori Richter and Thomas Friedli know a lot about that – you had a lot of conversations about operational excellence earlier this week (at a workshop sponsored by St. Gallen)

Operational Excellence started with quality. Juran was big on that in Japan, and Deming was as well. Deming is known to have said, “If you improve quality then decreased costs will follow.”

Unfortunately, in my experience – it actually shows in that little survey we did – most companies today are focused on cost reductions. And many times, it is short-term cost reductions.

I had an example in one of the facilities that Holger and I worked on. Procurement was buying raw materials, and they saved $2m a year. So they got bonuses, and everything was wonderful. But then we threw away $8m of product at the other end because the quality of the raw materials was not good enough.

So we need to think of a systems approach. We need to think end-to-end. And we need to think long-term. And I think what we need also, is what Holger spoke about earlier – we need to create that framework where people want to do quality improvement projects.

That is one of the things Deming was known for. Hundreds of thousands of small projects that all add up. So I think we need to have a much better focus on operational excellence from the quality perspective.

Because the opposite doesn't count. It is not that you decrease costs, and good quality will follow. It is actually the opposite, very often, right? You cut corners.

Quality as a Value-Driven Financial Advantage

So this is my summary: I think quality business leaders have a huge opportunity to enhance how we understand running a business. And it is not about quality only. It is about quality and financials. It is not one or the other. It is both of them that we need to think about.

Of course, we can't compromise quality. But it does require that we learn to speak in financial terms. What does a deviation cost? For an investment, what does that mean in terms of return on investment? So this speaks to many of the things that Jane was talking about as well.

It starts with knowing where the money goes. The two enablers ● quality risk management, and ● knowledge management are both really useful for this – to improve knowledge, reduce risk, and improve financial performance. And then there is that piece on operational excellence.

So, it is all about how we look at things and learning to speak the same language.