IPQ
INTERNATIONAL PHARMACEUTICAL QUALITY
Inside the Global Regulatory Dialogue

CURRENT INSIGHTS FROM LEADING REGULATORS

FDA Office of Compliance's Brooke Higgins Reviews Recent Inspectional Trends in Aseptic Manufacturing and Path Forward

At the May 2024 PDA Good Aseptic Manufacturing Conference, FDA drug compliance official Brooke Higgins discussed recent FDA inspectional trends in aseptic manufacturing. Higgins addressed three areas where the agency continues to see problems: ● aseptic technique ● cleanroom behaviors, and ● design of the aseptic processing area. She offered insights on learnings from FDA warning letters and the path forward. [See p. 3. Click HERE for previous Weekly Supplements.]

UPDATES IN BRIEF: GLOBAL CMC/GMP DEVELOPMENTS

● CDER 2023 Report on New Drugs Regulatory Program Modernization ● EU Recommendations to Tackle Shortages of GLP-1 Receptor Agonists ● FDA Guidance on EDDOs for Combination Products ● USP June Announcements include Revised Chapter on Drying ● EDQM 2023 Annual Report ● HMPC May 2024 Meeting Report on EU Herbal Monographs and Other Activities

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FDA DRUG GMP WARNING LETTERS

Company	Facility Location	Product Type
Sani-Care Salon Products	Georgia	Finished

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EMA GMP NON-COMPLIANCE REPORTS

Company	Facility Location	Product Type
Wasdell Europe	Ireland	Finished
Amara Labs	India	API

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FDA DRUG RECALLS

Among the eight recalls posted in FDA's enforcement report during the week, none drew the most serious, Class I, rating.

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OTHER IPQ CONTENT RELEASED DURING THE WEEK

Also released during the week was Part IV of IPQ's in-depth story on how the ICH goal of evolving its quality guideline series to better support innovation has continued to be realized in 2023 and 2024. Part IV focuses on the role of ICH's new cell gene therapy discussion group (CGTDG).

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INTERNATIONAL PHARMACEUTICAL QUALITY provides in-depth coverage of emerging drug, biologic and combination product CMC and GMP issues and developments with a mission of helping advance and harmonize the quality regulatory process globally. Headquartered in Washington, D.C., IPQ is read by regulatory agencies, manufacturers, suppliers, consultants, law firms, and universities around the world.

IPQ tracks the industry/regulator dialogue at key international forums along with the developments, initiatives, regulations, guidances and standards in the quality regulatory arena to create a uniquely valuable resource for the intelligence gathering and knowledge management needs of the pharmaceutical community.

IPQ's "actionable intelligence" is particularly valuable for thought leaders and decision makers who need to have a deeper understanding of the issues and their context to help shape regulatory policy and develop implementation strategies. Subscriber support allows IPQ, in turn, to make an important contribution to the efforts of key non-profit associations and public service organizations engaged in addressing the increasingly complex manufacturing and regulatory challenges for medicines in the global context.

IPQ is published online, and the substantial archive at IPQ.org is easily searchable through its keyword search indexes. Links to documents referenced and cross-links to related previous IPQ coverage in the area are included, allowing readers to quickly dig as deeply into an issue and its context as needed.

IPQ's ***"News Alerts"*** provide links to the first few paragraphs of the stories newly posted online. Subscribers and license holders can click through to the full stories.

The ***"Monthly Updates"*** provide the stories that went online during the month in a print-friendly PDF format, and are an easy way for subscribers to keep up with the critical developments impacting the quality regulatory process worldwide. Included are ***"Updates in Brief"*** on recent CMC/GMP developments of note with links to the referenced documents and to our related in-depth analysis. Also included is an annotated listing of FDA drug GMP warning letters and recalls as well as EU GMP non-compliance statements posted during the month.

IPQ INTERNATIONAL PHARMACEUTICAL QUALITY
Inside the Global Regulatory Dialogue

FDA Office of Compliance's Brooke Higgins Reviews Recent Inspectional Trends in Aseptic Manufacturing and Path Forward

At the closing plenary session of the PDA Good Aseptic Manufacturing Conference held in Stuttgart Germany in mid-May, FDA Center for Drug Evaluation and Research Office of Compliance Office of Manufacturing Quality Branch Chief Brooke Higgins reviewed recent inspectional trends in aseptic manufacturing and offered advice on remediation plans for companies that identify similar issues.

> **Higgins stressed that control strategies should be "living and updated regularly based on newly acquired data." She also suggested having an "open mindset" in looking for ways to improve.**

Touching on related areas to those discussed by EU regulators in the opening session ***(see IPQ Weekly Supplement for the week ending June 21, 2024)***, she pointed out the potential contamination hazards due to poor aseptic technique and facility design – affirming that she "sincerely" hopes "that we continue to strive towards increased separation and eventual elimination of personnel in sterile production operations."

Also stressing the need for and benefits of appropriate oversight, Higgins recommended "routine and meaningful observation of operator performance and aseptic technique during manufacturing operations" to pinpoint areas of improvement "through the lifecycle of your facility."

> **"Properly designed operations," she maintained, can "mitigate or eliminate" failure modes through "robust quality systems, effective quality risk management programs," and implementation of "appropriate contamination control and contamination prevention strategies."**

In terms of remediation plans, Higgins advised that risk assessments of aseptic processes, equipment, and facilities should be carried out by suitably qualified advisors and include but not be limited to: ● all human interactions within the ISO 5 filling area ● equipment placement and ergonomics ● air quality in the ISO 5 area and surrounding room ● facility layout, and ● personnel and material flows

Flaws in the design of cleanrooms and aseptic processing lines, or improper execution of aseptic operations, she noted, can promote the influx of contamination into the critical ISO 5 processing area, and the use of "antiquated facilities and designs" increases risk. Understanding and identifying the routes and sources of contamination "is crucial for effectively controlling them," she affirmed. ***[Higgins' full remarks are appended below.]***

Poor Aseptic Practices Continue to be Observed

Beginning her talk with a model of sterility assurance for aseptic processing developed by her Office of Compliance colleague, Rick Friedman, Higgins pointed to the "multitude" of variables and sub-variables that "require meticulous control," and noted that any lapses in control can have severe consequences. Robust quality risk management (QRM) is "imperative at the outset," she emaphsized, and FDA warning letters continue to identify similar trends in deficiencies.

[See IPQ April 29, 2021, for an in-depth review by Friedman on advancing aseptic processing through QRM, and the Weekly Supplement for the week ending June 7, 2024 for his insights on quality/operations/business synergies.]

Among the poor aseptic practices observed in recent inspections, Higgins pointed out, have been: ● operators performing critical interventions without using glove ports when they were available ● operators reaching over the filling line, breaking first air in critical areas ● inadvertent contact with the interior of filling cabinet or restricted access barrier systems [RABS] door, and ● RABS or filling cabinet doors left open for extended periods of time.

> **"It is concerning to see firms lapse from the state of control required by CGMPs. And despite their availability, I think many detailed resources and guidance documents go underutilized."**

Higgins then explained why personnel are the primary source of contamination and the "biggest risk for aseptic operations." However, she stressed, while comprehensive environmental and personnel monitoring programs are "essential" to obtain feedback on the state of control in the processing environment, "it is also critical to understand what you are dealing with in terms of the design – the gaps, the limitations, the hazards."

"Merely drafting different procedures, offering initial training, and leaving it at that is insufficient," she maintained. "Training should not be a one-time event, but rather an ongoing process that involves continual observation and regular feedback." ***[See IPQ February 20, 2024, for an in-depth analysis by former FDA official Stephen Langille of quality culture and oversight in aseptic operations.]***

Cleanroom Behaviors and Facility Design Draw Attention

During her presentation, Higgins used several photographs and videos collected from recent inspections to illustrate the inappropriate cleanroom behaviors being observed and how poor design causes difficulties for operators.

After one video in particular, she asked, "Where was the oversight?" and demonstrated in another that the observation window only showed a very limited view of the aseptic processing area.

> **To ensure proper cleanroom practices, she asserted, "collaboration between personnel and management is crucial." Whether in the initial setup, processing, or cleaning, quality management and cleanroom personnel "must remain vigilant to ensure that contamination control measures are effectively implemented."**

Regarding the design of the aseptic processing area, Higgins shared examples of poorly designed setup – both from within the pharma environment and outside it. Inspectors have been identifying "numerous deficiencies" in design. The question is: "Is the line designed in a way that enables operators to efficiently carry out interventions, or are we simply setting our operators up for failure?"

She listed some of the factors that inspectors consider when evaluating line design and reiterated the QRM principles of ICH Q9 "to really drive this point home." ***[See IPQ September 25, 2023, for insights from the ICH Q9(R1) revision from the rapporteur for the Expert Working Group.]***

Moving on to discuss "thoughtfully designed barriers," Higgins linked her earlier discussion on the extent of human skin and bacteria shedding to the need for separation of personnel from the products on an aseptic filling line. She shared a graphic comparing what was typical in the 20th century and "where we ideally should be a quarter into the 21st century."

> **Considering the available technologies today, relying on "antiquated lines should not be the default choice for new facilities," she asserted. "Moreover, older facilities should undergo assessments for upgrades to transition away from lines that pose elevated risks of quality and safety failures."**

Again, to back up her assertions, Higgins shared photographs and videos of poor designs in older lines and where RABS have been inappropriately retrofitted into unsuitable spaces. She also gave examples of where there was a clear misunderstanding of the term "open RABS."

Warning Letters Can Be Used as Roadmap for Improvement

In closing, the FDA official advised utilizing the agency warning letters as regulatory intelligence. Performing a "comprehensive and systematic evaluation of the deficiencies" in them can provide an "initial roadmap" to addressing any similar deficiencies observed internally.

"Whether it is an open system or an isolator, it is crucial that you take the time to: ● comprehensively understand the hazards ● observe operations, and ● compare what is being done with what the established procedures require." Complementing Higgins' presentation were those given by EU GMP inspectors Daniel Mueller and Christina Meissner in the opening session of the May PDA Aseptic Conference.

EMA GMP Technical Lead Roberto Conocchia followed Higgins at the closing session with updates on Annex 1 from the European Inspectors Working Group and international perspectives from the Pharmaceutical Inspection Cooperation Scheme (PIC/S).

A closing panel discussion brought together current and former regulators and industry experts for a dialogue on Annex 1 and related aseptic processing issues and where further elaboration and clarification is needed.

[Editor's Note: The next IPQ Weekly Supplement will share insights from the presentation given by EMA's Conocchia. Selected comments from the panel discussions in both the opening and closing plenary sessions of the conference will be included in an upcoming IPQ story.]

[Subscribers CLICK HERE for Higgin's complete remarks at the PDA conference.]

IPQ'S IN-DEPTH COVERAGE RELEASED SINCE 2020

The following are the headlines of the in-depth stories that IPQ has released since 2020. The topic headings for parts of a larger multipart story are included. The stories are listed in reverse chronological order. Readers of the Weekly Supplement can then click though to those that are of particular relevance to the regulator presentation, news briefs, and compliance information featured in the issue. Those of particularly high relevance to the Weekly regulator story are indicated with a red star.

2024

★ **The Challenges of Evolving Pharma from a Compliance to a Risk-Based Control Strategy Mindset Are Drawing Conference Spotlight**

- Critical Thinking in Risk Management and Data Governance
- Quality Culture/Oversight in Aseptic Operations
- Takeda's Annex 1-Based Global CCS Program
- QRM Tools in Root Cause Analysis
- Annex 1 Revisions and the CCS Implications

2023

CMC Innovation Support Programs Advance at EMA and FDA, with Distributed and Continuous Manufacturing on Front Burner

- European Regulatory Network Support for Manufacturing Innovation
- FDA's Expanding Engagement with Advanced Technologies
- Barriers to CM Adoption Explored at USP/RAPS Workshop
- Distributed/POC Manufacturing and the CMC/Quality Regulatory Paradigm

★ **Implementing ICH Q9(R1) Will Entail a Heightened Focus on Integrating Knowledge into Risk-Based Decision-Making**

- Insights from Expert Working Group Members on ICH Q9 Revisions
- Panel Discussion Among PRST Meeting KM/QRM Experts
- Risk-Based Decision-Making
- Risk Management in Drug Shortage Prevention

Industry is Urging EMA to Increase its Focus on Medicine Impact of EU Food, Chemical, and Environmental Legislation

- The Need for Pharma Stakeholder Engagement
- EU PFAS Action and Pharma Mitigation Needs
- Industry and EMA on F-gases and Hydrofluorocarbons in Inhalation Products
- DIA Europe Legislative Session Panel Discussion
- Intensified Industry Dialogue on TiO2 and Nanoparticles Ahead of More EMA Review

IPEC is Helping Marshal Expertise Across Stakeholders to Forestall a Potential TiO_2 Ban in Pharmaceuticals

USP Continues to Refine Its Strategies for Keeping Pace with and Supporting the Rapidly Advancing Biotechnology in the MAb, Vaccine and CGT Arenas

- USP Bio Stakeholder Forum Opening Remarks and Mass Spec Standards for Proteins
- USP's CGT Initiatives
- FDA and Industry Experience with CAR T Potency Testing
- Update on USP Strategies and Initiatives in the MAb, Vaccine, and CGT Arena

Government/Industry/Academia Collaborative Efforts to De-Risk and Accelerate Manufacturing Innovation Draw Strength from Pandemic Learnings

- NIIMBL and its "Going First Together" Mantra
- US Manufacturing Innovation Leaders Weigh In
- The Importance of Process and Facility Innovation in Global Health
- Charting the Advanced Therapy CMC Pathways and Other NIIMBL Projects
- CBER's Marks on Taking CGTs to the Next Level

ICH Q3D Implementation Continues with Workshops, Research, and Guideline and Pharmacopeial Revisions

- Role of PQRI/FDA Workshop in Q3D Implementation Dialogue
- Regulatory Experience and Perspectives in Implementing Q3D
- Pharmacopeial Harmonization with ICH Q3D
- Outcomes of PQRI Study on Variability in Elemental Impurity Analysis

2022

Strengthened European Regulator Support for Advanced Technologies Includes New EMA Quality Innovation Group

- Europe's Focus on CMC Innovation and Agile Regulation
- Innovation Issues Explored at CASSS CMC Forum in Europe
- MHRA's "New Era in Regulation"

EMA Toolbox on CMC Flexibilities has been Evolving to Incorporate Industry Input and Learnings from the Pandemic

- EMA Perspective on its Toolbox Guidance and OPEN Initiative
- Industry View on Efficiency Tools and CMC Flexibility Learnings from COVID
- Panel Discussion on Effective Tools for the Future

CBER's Advanced Technologies Program Growing Stronger with Increased Funding, Expertise, and Collaboration

mRNA-LNP Vaccines Spur Global Dialogue on Nanomaterial Standards and Regulatory Approaches

- Pfizer/BioNTech Lipid Challenges with mRNA-LNP COVID Vaccine
- FDA's Novel Excipient Review Pilot Program and Nanomaterials Guidance
- USP's Draft Guideline and Other Efforts on mRNA Vaccine Quality
- The EDQM Nanomedicines Dialogue and WHO on Regulating mRNA Vaccine Quality
- Potency Assays for mRNA-LNP Vaccines

NASEM-Led Study for FDA is Helping Drive Industry/Regulator Agenda on Innovation Needs

- The NASEM Study and FDA Reflections
- Existing Mechanisms to Enable Innovation
- Challenges and Opportunities
- The Path Forward

Pandemic Experience Showcases the Potential for Faster Innovation, More Collaboration, and Workplace and Operations Modernization

- The Evolving Landscape of Pharmaceutical Operations
- Government-Industry Collaboration in This and Future Pandemics
- Reducing the Cost of Vaccine Manufacturing for Broader LMIC Access

Progress in Addressing Impurity Challenges in Focus at USP's 2022 Peptide/Oligo Workshop

- US and European Regulator Perspective on the CMC Challenges of Oligonucleotides
- USP Standards Development Efforts for Peptides and Oligos
- Peptide and Oligo Analytical, Manufacturing and Raw Material Considerations

Pandemic Experience and Supply-Chain Risk Management Expectations Increase Attention on Excipient GMP Third-Party Auditing

Janet Woodcock and Jeff Baker will Continue to Play Key Manufacturing Innovation Roles in New FDA and NIIMBL Positions

FDA's KASA and Related PQ/CMC Initiatives on Improving CMC Data Structuring and Sharing Will Help Support ICH M4Q Revision

- The Advancing Knowledge-aided Assessment Component of KASA
- Bringing Biologics into the KASA System
- The Progress of FDA's PQ/CMC Initiative
- The Goals of Accumulus Synergy in CMC Data IT and Regulatory Communication
- The Drivers for Revising ICH M4Q and Evolving the CMC Regulatory Process

Key GMP Focal Points in Europe Include Guidance Revisions, New Vet Regulations, and Adaptive Assessment/Inspection Approaches

- Update on EMA GMP-related Activities
- MHRA Innovation Pathway and Proposal for Point-of-Care Regulatory Framework
- Insights from Europe and ICMRA Regarding Onsite Inspection Alternatives

2021

USP and Ph. Eur. Initiatives in the Biologics Arena Continue to Bear Fruit; FDA Joins the Pharmacopeias in Upgrading Particulate Guidance

- Update on USP's Evolving Role and Current Initiatives In the Biologics Arena
- European Pharmacopoeia and FDA Join USP in Focusing on Particulate Control

COVID Vaccine Industry Project Leaders Are Sharing Insights on How the Daunting CMC Challenges Were Addressed

- Implementing the Pfizer/BioNTech mRNA Vaccine Development Plan
- New Digitalized Facility as Springboard for Moderna's mRNA Vaccine
- Oxford University/AZ Partnership for Global Adenovirus Vaccine Access
- J&J's Experience in Handling the Supply Chain Challenges
- Novavax's Approach to Assuring Comparability for its Protein-based Vaccine
- Inter-Company Panels at DIA and ISPE Meetings on Vaccine Experience

Biomanufacturer Raw Material Control on Regulatory Front Burner as Analytical Power and Formulation Challenges Intensify

- Biotech Regulator Vantage Point on Raw Material Control
- The Added Challenges of Materials Management for CGTs
- Biomanufacturer Use and Control of Polysorbates

Manufacturing, Impurities, and Characterization Methods Are Key Regulatory Focal Points for Peptides and Oligonucleotides

- Recent CMC/Regulatory Challenges of Oligonucleotide Drugs
- Comparability Challenges in Crossing Over to Generics
- Comparing Peptide and Oligonucleotide CMC Issues
- Starting Material Specifications for Oligonucleotides

A Confluence of Forces Is Now Spurring Combination Product Regulatory Reform in Europe

- EU Pharma Strategy Roadmap, Comments from Industry, and Related Agency Strategies
- Culture/Structure/Process Change and Global Alignment
- HPRA CEO Lorraine Nolan on HPRA and EMA Strategy
- EMA's Zaïde Frias and NB/Industry Perspectives on EU Regulatory Transformation

Pandemic Urgencies Highlight Constraints in Manufacturing Change Regulatory Paradigm and Where Adjustments Are Needed

- Industry Quality Leaders on the Global PAC Regulatory Problem and Solutions
- Evolving the Quality Regulatory Paradigm at the Global Level

★ **Regulators Are Exploring with Industry How to Strengthen Quality Risk Management Practices, with Revision of ICH Q9 a Key Focal Point**

- ICH Q9 Revision Lead O'Donnell on the Evolution of QRM
- FDA's Rick Friedman on Advancing Aseptic Processing through QRM
- Industry/Academia Thought Leaders on the Evolving QRM/KM Relationship

Regulators Share Pandemic's CMC Impact at CASSS Japan Forum; Guidance Output Continues Apace in Q1 2021

- EMA Perspective
- FDA CBER Perspective
- FDA CDER Perspective
- Panel Discussion Among US, Europe, and Japan Regulators

Academia/Industry Collaboration Intensifies on Addressing the Pressing Needs in Biopharma Workforce Development

- NIIMBL's Engagement with Academia on Workforce Development Needs
- ISPE Workforce of the Future Traction at UMBC and UC Davis
- Keck Institute's Behrens on Biopharma Talent Needs and KGI/Industry Partnering
- Xavier's Phillips on Sharable Quality and Regulatory Science Curriculum
- CASSS Panel on Opening Up Biopharma Career Pathways
- European and Global Workforce Development Collaborations

Latest Improvements in FDA's Inactive Ingredient Database Include Change Log and Use of Maximum Daily Exposure

Recent Technology and Partnership Advances Made Possible Precision and Speed of Vaccine Response to Pandemic, NIAID's Graham Stresses at CASSS WCBP Conference

Pandemic Intensifies USP's Focus on Supply Chain Vulnerabilities and Vaccine Development

2020

Pandemic Spurs Deepening of Pharmacopoeia/Regulator/Industry Communication Channels

- EDQM Pandemic Actions Continue Apace in Fall 2020
- Pharmacopeia, Regulator and Industry Expert Panel Explores Pandemic and Nitrosamine Communications
- Second Panel Focuses on Pandemic Organizational Impacts and Key Learnings
- EDQM and Ph. Eur. Evolution Addressed by Leaders Keitel and Vielle

COVID Vaccine Global Distribution Challenges Explored by Bio Supply Management Alliance (BSMA) Panel of European Experts

Pandemic Stresses Increase FDA Attention on Risk Management Plans for Drug Shortage Prevention and Mitigation

USP's Global Efforts to Strengthen Standards and Accelerate Innovation for Biologics Include ICH Engagement

CBER Director Marks Traverses the Complex COVID-19 Vaccine/Therapy Regulatory Landscape at FDLI's Annual Conference

Stronger Unapproved Stem-Cell Enforcement Accompanies FDA Center for Biologics' Cell and Gene Therapy Advancement Efforts

Design-Based Development Paradigm for Cell/Gene Therapies Will Significantly Reduce Costs, Timelines and Regulatory Concerns, AGT CEO Galvin Maintains

Synthesis and Analysis Advancements Are Unleashing the Potential of Peptides and Oligos, Spurring CMC Regulatory Dialogue

USP Convention Meets Virtually in May 2020 to Review Upcoming Priorities, with Both 200-Year Legacy and Current Pandemic in Focus

COVID-19 Vaccine Urgency Throws Spotlight on Next-Gen Sequencing as Key Facilitator

- Adventitious Agent Testing in Focus at CASSS CMC Forum Europe
- Sanofi Pasteur and Ghent University Experience with NGS
- A Decade of Regulator/Industry Collaboration on NGS
- Stakeholder Engagement Begins on ICH Q5A Revision
- Effort to Reduce Animal Testing for Vaccines Includes Global Health Fund Support for NGS

NIIMBL Progress Includes Partnership with Biophorum on Buffer Mixing and Global Health Fund with Gates Foundation

★ Top FDA Drug Compliance Concerns during 2019 Included OTCs, Supply Chain Information Flow, Compounding, and Genotoxic Impurities

Existing Accelerated CMC, Advanced Manufacturing, and Inspection Initiatives are Supporting Regulators in Pandemic Response, FDA's Cruse Explains in Recent Field Office Updates

Attention Heightens on Creating an Independent Regulatory Pathway for Introducing Novel Excipients

- FDA'S Novel Excipient Program Proposal and Stakeholder Comments
- IPEC/IQ Thought Leaders on the Novel Excipient Drivers
- Subcutaneous Biotherapeutics, Pediatrics, and Delayed Release
- USP Initiatives Supporting Novel Excipient Development
- Assessing and Managing Excipient Risks

US/EU MRA Implementation, US Congressional Hearings, and Industry Surveys Shed Light on Global GMP Inspection Challenges and Collaboration Opportunities