IPQ
INTERNATIONAL PHARMACEUTICAL QUALITY
Inside the Global Regulatory Dialogue

CURRENT INSIGHTS FROM LEADING REGULATORS

FDA's Lawrence Perez Reviews Key CMC Challenges for Synthetic Oligonucleotides at USP Peptide/Oligo Workshop

At the opening session of the 2024 USP peptide/oligo workshop, held at USP's Rockville, Maryland headquarters in April, FDA Office of Pharmaceutical Quality (OPQ) Senior Pharmaceutical Quality Assessor Lawrence Perez discussed the CMC challenges the agency has been seeing in reviewing synthetic oligonucleotide therapeutics. His presentation covered: • defining synthetic oligos, and the different classes that have been approved • the specification of the API's identity, purity, and assay, and • manufacturing issues, including starting materials, API sameness for generics, and platform technologies.

UPDATES IN BRIEF: GLOBAL CMC/GMP DEVELOPMENTS

• TGA Update on Nitrosamine Impurities Acceptable Intakes • DRAP Post-Registration Variation Guidelines for Pharmaceutical and Biological Products • FDA FY 2022 Annual Report on the Status of PMRs and PMCs • EMA Recommendations to Strengthen Supply Chains of Critical Medicines • FDA Udated Biosimilars Action Plan, and BsUFA Milestone • FDA Guidance on Composition Statements and Corresponding Labeling in NDAs and ANDAs • USP April Announcements, including New Chapters on Iron Colloidal and Microsphere Products • APIC Best Practices Guide for Managing Suppliers of API Manufacturers, and 2023 Annual Report • Philippine Guidelines on Import/Export Notifications for Drug Products and Raw Materials

FDA DRUG GMP WARNING LETTERS AND EMA NCRs

There were no FDA drug GMP warning letters nor EMA non-compliance reports posted during the week.

FDA DRUG RECALLS

Among the six recalls posted in FDA's enforcement report during the week, two drew the most serious, Class I, rating. One of these involved one lot of non-sterile product, atovaquone powder, for potential *Bacillus cereus* contamination. The second recall involved four lots of superpotent vancomycin liquid due to the overfilling of drug powder.

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.

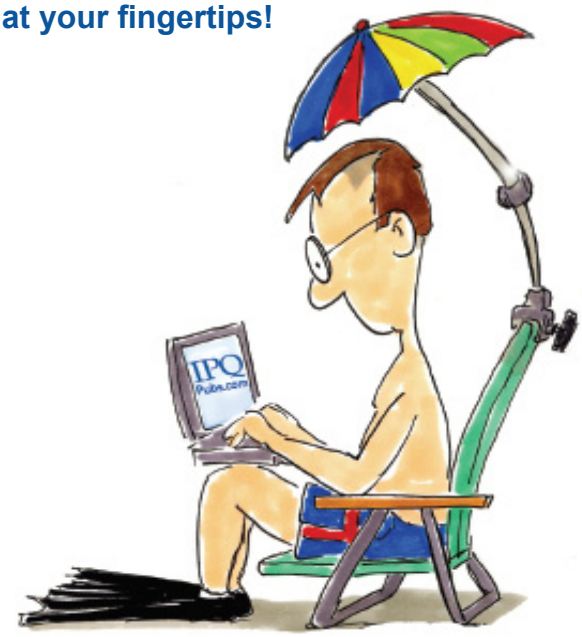
IPQ's "actionable intelligence" is particularly valuable for thought leaders and decision makers who need to have a deeper understanding of the issues and their context to help shape regulatory policy and develop implementation strategies. Subscriber support allows IPQ, in turn, to make an important 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.

From breaking news to in-depth analysis — the quality regulatory intelligence you need at your fingertips!



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IPQ takes Its readers from:

- **headlines to the forces driving them**
- **regulations to their underlying intent**
- **puzzle pieces to their interconnection**
- **rules to implementation pathways**
- **random data to critical trends**
- **the sidelines to shaping the outcome**
- **compliance problems to proactive tools**
- **information to strategic intelligence**

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FDA's Lawrence Perez Reviews Key CMC Challenges for Synthetic Oligonucleotides at USP Peptide/Oligo Workshop

FDA's experience with reviewing applications for synthetic oligonucleotide therapeutics indicates that the specification of the API is a key CMC issue on which sponsors need to pay close attention.

> **Speaking at the opening regulatory/compendial session of the USP peptide/oligo workshop, held at USP's headquarters in Rockville, Maryland in early April, FDA CDER Office of Pharmaceutical Quality (OPQ) Senior Pharmaceutical Quality Assessor Lawrence Perez highlighted the CMC challenges that the agency has been seeing in reviewing synthetic oligos.** ***[Perez' full remarks are appended below.]***

He noted that discussions with developers have centered, in particular, on the specifications for the API's identity, purity, and assay.

Perez opened the presentation by offering a regulatory definition of synthetic oligos and describing the three different types of the 18 that have thus far been approved – aptamers, antisense oligos, and siRNAs.

FDA Requires Oligo-Specific Methods for the API Specification

The CDER reviewer acknowledged that the identity test in the specification for synthetic oligos is "a gray area." Due to their large size and polymeric composition, typical identity tests for small molecules – molecular weight, retention time/spectroscopy – "do not really address all the nuances for the oligos."

As such, FDA requires the addition to the specification of an identity-by-sequence test. The merits and limitations of the melt temperature test, failure sequence analysis test, and mass spec/mass spec analysis were described.

Drug purity is a further focus for FDA discussions. Perez cautioned that for oligos, there is not just one compound under the individual peaks in a chromatogram, as impurities are isolated along with the main peak.

> **In order to demonstrate that impurity profiles are under control, FDA recommends that applicants group the impurities – either by molecular weight or by retention time.**

The impurity profile for siRNA, being double-stranded, presents further particular CMC issues. For siRNAs, FDA requires two purity tests, using both denaturing and non-denaturing conditions.

For synthetic oligos, the standard assay is a weight-based test and Perez acknowledged the difficulty for developers in performing this assay given that a highly purified reference standard is required, which may be in short supply early in the drug development process.

> **He went on to confirm that a cell-based assay is not required for antisense oligos and siRNAs because their biological activity is primarily determined by their primary sequence – which is characterized in any case as part of their identity test.**

The CDER reviewer stressed, however, that aptamers may need justification for not using a cell-based assay, given that these molecules may have a conformational aspect to their biological activity. In this case, additional conformational data – for example, circular dichroism or 2D NMR – may be required.

Starting Materials, API Sameness, and Platform Technologies are Key Manufacturing Issues

Turning to manufacturing, Perez explained how the process is not typically an issue for regulators, given that this is a mature technology developed back in the 1980s.

Instead, questions focus on the designation of the regulatory starting materials. FDA is satisfied that the common starting materials used in oligo synthesis are available with high purity from a variety of manufacturers. However, FDA is increasingly seeing novel starting materials, such as the conjugated GalNAc phosphoramidites, and compliance with ICH Q11, Perez stressed, is required for such novel materials.

He then turned his attention to the issue of API sameness – an area of increasing importance to FDA given the emerging interest in generic synthetic oligos in recent years.

For phosphothiolate analogs, the manufacturing cycle produces stereogenic centres, resulting in the production of diastereomeric mixtures. Perez acknowledged that this raises significant analytical challenges for developers to demonstrate that the diastereomeric composition of the generic oligo is the same as that of the reference listed drug.

Platform manufacturing and the use of platform data were then addressed – topics of recent importance for FDA in the wake of Congress' amending of the Food, Drug and Cosmetic (FDC) Act to recognize a category known as "designated platform technologies." The subject will be explored in an upcoming draft guidance that the agency is planning to release for comment by the third quarter of this year.

FDA Releases Guidance on CMC information in Antisense Oligo INDs

Perez acknowledged that FDA has not published a specific guidance for the commercial development of synthetic oligos.

Four guidances have recently been published addressing the development of individualized (N-of-1) oligonucleotides during the IND phase. One of the four provides recommendations for CMC information in INDs for antisense oligos. The other three deal with clinical, non-clinical, and administrative aspects, respectively.

The OPQ reviewer concluded by strongly encouraging applicants to have a discussion with FDA when any of these CMC issues arise.

During the Q&A that followed the FDA and USP presentations at the oligo/peptide workshop, Perez responded to a question on the analytical challenge for generic oligo developers to demonstrate pharmaceutical sameness given the number of diastereomeric mixtures that can be produced in the oligo manufacturing process.

He commented that therapeutic equivalence is based on both pharmaceutical equivalence and bioequivalence. The objective of the various tests is to ensure that the generic oligo is as safe and as effective as the reference listed drug.

In situations where analytical techniques are not sufficient to establish pharmaceutical equivalence, the regulator advised that it may be possible to use other physical techniques or gain the necessary information from a bioequivalence study.

Opening Peptide/Oligo Session Also Explores USP, FDA Peptide, and EMA Initiatives

Also presenting at the opening session of the USP peptide/oligo workshop were: ● USP Biologics Science & Standards Senior Director Kevin Carrick, who spoke on the pharmacopeia's current engagement with the products and its related standards initiatives ● FDA OPQ Senior Pharmaceutical Quality Assessor Katherine Duncan – addressing the CMC regulatory experiences and expectations for peptides, and ● Germany Federal Institute for Drugs and Medical Devices (BfArM) CMC Reviewer and Pharmaceutical Biotechnology Unit Deputy Head Rene Thürmer, who reviewed the European quality guidelines and initiatives for synthetic peptides and oligos.

Four sessions followed at the two-day workshop that brought in industry experts to further explore the issues around starting materials, analytical technologies, manufacturing strategies, and impurity control, respectively.

[Editor's Note: See IPQ May 10, 2022, for an in-depth review of the previous USP peptide/oligo workshop, held in March 2022. IPQ will be adding to Perez' discussion of synthetic oligonucleotides with more on this year's workshop in an upcoming story, which will include a full review of the peptide/oligo presentation by USP's Carrick and that on peptides by FDA's Duncan.]

LINKS:

- FDA IND CMC Guidance for Individualized Antisense OIigos

[Subscribers CLICK HERE for Perez' complete remarks at the USP Workshop.]

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