IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

2022 Summary:

Global Developments in OINDP Regulations & Standards

About IPAC-RS

The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) is an international association that seeks to advance the science, and especially the regulatory science, of orally inhaled and nasal drug products (OINDPs) by collecting and analyzing data, and conducting joint research and development projects. Representing the OINDP industry since 2000, IPAC-RS aims to build consensus and contribute to effective regulations and standards by sharing the results of its research through conferences, technical journals, webinars, and discussions with regulatory bodies.

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I. Developments in Regulation & Standards

Brazil

- Anvisa held a webinar with medicines associations, addressing remote inspections and the Agency's work in the context of *Pharmaceutical Inspection Co-operation Scheme* (PIC/S) requirements; and the ICH harmonization process.
- Anvisa issued the Brazilian Pharmacopoeia Work Program for public consultation.
- Anvisa issued a Resolution establishing a pilot for implementation of the post-approval change management protocol for drugs with synthetic and semi-synthetic active ingredients, based on the ICH M12.
- Anvisa issued a Resolution on risk assessment and control of potentially carcinogenic nitrosamines in Active Pharmaceutical Ingredients (API) and drugs for human use.
- Resolution - RDC No. 753 provides for the registration of medicines for human use with synthetic and semi-synthetic APIs classified as new, innovative, generic and similar. A related Normative Instruction is also available.
- Resolution RDC No. 750 provides for a temporary process in which reviews conducted by an Equivalent Foreign Regulatory Authority are used for analysis of registration and post-registration petitions.

China

- The China National Pharmaceutical Packaging Association (CNPPA) developed the Guidelines for Research on Equivalence/Substitutability and Compatibility of Marketed Drug Packaging Changes (T/CNPPA 3019-2022).
- The CDE issued a draft guideline for public comment, addressing procedures for the CDE to accelerate the review of innovative drug marketing applications.
- The CNPPA, with the help of USP, EDQM, IPAC-RS, and some companies, translated 'Compatibility of Pharmaceutical Products and Contact Materials', 'Leachable & Extractable Handbook', 'Selections of Pharmaceutical Packaging Materials Standards from USP, EP and JP', and published the technical book 'Theory and Practice of Drug and Packaging Compatibility'.
- The CDE issued a guideline addressing the general format and writing of instructions for chemical drugs and therapeutic biological products.
- The China Center for Medical Device Evaluation posted a summary of the first meeting of the Artificial Intelligence Medical Device Innovation Cooperation Platform Management Committee.
- The National Medical Products Association (NMPA) issued a draft guideline on Good Manufacturing Practice for Pharmaceutical Packaging Materials.
- The NMPA issued the 2021 Annual Drug Evaluation Report.
- The 12th Chinese Pharmacopoeia Committee was established to prepare the 2025 edition of the Chinese Pharmacopoeia.

- Inhalable COVID-19 vaccine was administered in China.
- The China National Pharmaceutical Packaging Association (CNPPA) held its 2022 Suzhou Dialogue in August. Sessions included:
  - "Chinese Pharmacopoeia in Reform - Knowledge and Adaptation of Pharmaceutical Packaging Material Standards."
  - "Drug Packaging Safety and Sustainable Development."
  - "Supply Chain Industry Chain and Modernization of Pharmaceutical Packaging", and "Inhalation Formulation Forum."
  - "Risk control and research on auxiliary materials and packaging materials."
- The NMPA issued the Measures for the Administration of Drug Recalls, which is the first revision of its approach on recalls since 2007. Information can be found here. "Quick facts" regarding the measures are also available here.

Europe

- EMA issued a guidance on scientific advice and protocol assistance.
- EMA issued Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorization applications targeting an unmet medical need.
- European Environment Agency published an updated report on air quality which identified air pollution as the most serious single health risk.
- EMA published a new iteration of its Q&A document, Nitrosamines EMEA-H-A53)-1490 - QA Art. 5(3) Implementation for July CHMP CMDh - (QA3).
- The European Fluorocarbons Technical Committee (EFCTC) issued a survey on F-gases.
- EMA published an article summarizing the use of real-world evidence to support efficacy/effectiveness.
- The EU Court of Justice partially overturned the 2019 restrictions on TiO2 (titanium dioxide).
- The European Council gave their support for the European Commission's proposal to delay the transitional deadlines for medical devices under MDR. The proposal was made to extend deadline for higher risk class III and class IIb devices to 2027, and deadline for lower risk class I and class IIa devices to 2028.

International

- US FDA, Health Canada, and UK's MHRA agreed on principles for a future guidance on machine learning.
- Revised draft ICH Q9, on Quality Risk Management, was issued for public consultation.
- Model informed drug development was named the subject of an informal ICH working group and has been provided the ICH code M15.
- Two guidelines were published by ICH for public comment:
  - ICH_Q14_Document_Step2_Guideline_2022_0324.pdf.
  - ICH_Q2-R2_Document_Step2_Guideline_2022_0324.pdf.
- International Medical Device Regulators Forum (IMDRF) invited comments on their Principles and Practices for the Cybersecurity of Legacy Medical Devices.
- ICH adopted the Q13 guideline on continuous manufacturing (CM) of drug substances and drug products, which clarified state of control and included a revised definition of process dynamics.

Japan

- PMDA participated in a joint forum of regulators and auditing organizations on the international Medical Device Single Audit Program (MDSAP).
- PMDA posts updates here regularly.
- PMDA posted an English version of its guideline on Procedure for Remote Inspection as a Part of Compliance Inspection on Drugs and Regenerative Medical Products.
- PMDA participated in the annual IMDRF Management Committee meeting, where guidance for Personalized Medical Devices – Regulatory Pathways and guidance for Personalized Medical Devices Production Verification and Validation were approved as public consultation documents.

United Kingdom

- The UK Medicines and Healthcare Products Regulatory Agency (MHRA) joined the International Medical Device Regulators Forum, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, and the Medical Devices Innovation Consortium.
- MHRA published updated information about combined review of investigational medicinal products.
- MHRA updated its Guidance on the licensing of biosimilar products.
- MHRA published an updated document on the Software And AI as a Medical Device Change Program.

United States

Congress

- The US government published a list of proposed rules as a collaboration between several agencies, including the FDA.
- Publications from all US federally-funded research will be required to be provided in open-access starting no later than 2026.
- US Senate ratified the Kigali Amendment to the Montreal Protocol: Statement by President Joe Biden on Senate Ratification of the Kigali Amendment to the Montreal Protocol.

U.S . Food and Drug Administration (FDA)

- FDA accepted comments on the discussion paper, 3D Printing Medical Devices at the Point of Care.
- FDA CDER 2022 Guidance agenda.
- Draft FDA Guidances published for comment including:
  - Digital Health Technologies for Remote Data Acquisition in Clinical Investigations.
  - Referencing the Definition of "Device".
  - Aclidinium/Formoterol DPI - Draft Product-Specific Bioequivalence Guidance.
  - Sodium Chloride Metered Inhalation Aerosol - Draft Product-Specific Bioequivalence Guidance.
  - Digital Health Technologies for Remote Data Acquisition in Clinical Investigations.
  - Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions
  - Revising ANDA Labeling Following RLD Labeling Revision.
  - Identifying Trading Partners Under the Drug Supply Chain Security Act and DSCSA Standards for the Interoperable Exchange of Information for Tracing of Certain Human, Finished, Prescription Drugs Guidance for Industry.
  - Benefit-Risk Considerations for Product Quality Assessments.
  - Fostering Medical Device Improvement: Food and Drug Administration Activities and Engagement with the Voluntary Improvement Program.
  - Computer Software Assurance for Production and Quality System Software.
  - Q3D(R2) – Guideline for Elemental Impurities.
  - Content of Human Factors Information in Medical Device Marketing Submissions.
  - Voluntary Malfunction Summary Reporting (VMSR) Program for Manufacturers.
  - Statistical Approaches to Establishing Bioequivalence.
  - Risk Management Plans to Mitigate the Potential for Drug Shortages.
  - New product-specific bioequivalence guidances: Flunisolide nasal spray and Naloxone Hydrochloride nasal spray.
  - Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments.

- Final FDA guidances published including:
  - Good ANDA Submission Practices.
  - Population PK.
  - Principles of Premarket Pathways for Combination Products.
  - Patient Engagement in the Design and Conduct of Medical Device Clinical Studies.
  - Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation.
  - Electromagnetic Compatibility (EMC) of Medical Devices.
  - Drug Products, Including Biological Products, That Contain Nanomaterials.
  - Product labeling to reduce risk of medication errors.
  - Electronic Submission Template for Medical Device 510(k) Submissions.
  - Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.
  - Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA.
  - Referencing the Definition of "Device" in the Federal Food, Drug, and Cosmetic Act in Guidance, Regulatory Documents, Communications, and Other Public Documents.
  - Format and Content of a REMS Document Guidance for Industry.
  - Post-Approval Changes to Disposable Manufacturing Materials: Questions and Answers Guidance for Industry.
  - New product specific bioequivalence guidances for Desmopressin metered nasal spray, Flunisolide metered nasal spray, Fluticasone metered nasal spray, Formoterol / Glycopyrrolate pMDI, Glucagon nasal powder, Levodopa inhalation powder, Loxapine inhalation powder, Mannitol inhalation powder, Tobramycine inhalation powder, and Zanamivir inhalation powder.
- FDA published a 127-page report of science research conducted under GDUFA in 2021.
- FDA solicited comments on adding maximum daily exposure (MDE) information for inactive ingredients and whether to restructure CDER's Inactive Ingredient Database (IID) by removing dosage form information.
- FDA/OPQ issued a white paper "Quality Management Maturity" and conducted free public webinars to discuss the QMM concept and how it relates to ICH M12 and supply chain management.
- CDRH planned to return to normal pre-submission timelines.
- According to an FDA audit published in IJP and summarized by RAPS, applications using continuous manufacturing were approved faster than those relying on traditional batch approaches.
- FDA published a MAPP clarifying classification and examples of complex products.
- FDA's CDER launched the Accelerating Rare disease Cures (ARC) Program.
- FDA announced revisions to the 2006 guidance, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production.
- FDA published an article on the Effects of Realistic In Vitro Test Factors on the Aerosol Properties of Metered-Dose Inhalers.
- FDA published notice of Alternative or Streamlined Mechanisms for Complying with the Current Good

Manufacturing Practice Requirements for Combination Products: List under the 21st Century Cures Act.

- The Center for Research in Complex Generics (CRCG), established by FDA in 2020, conducted a survey of standards on nanotechnology.
- FDA received comments on its "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)."
- Bioequivalence and quality considerations for generic DPIs were published by FDA scientists in a special issue of Advanced Drug Delivery Reviews: Quality aspects, Bioequivalence aspects.
- FDA's device center published CDRH proposed guidelines for the fiscal year of 2023.
- FDA announced a pilot program to help companies streamline CMC development.
- FDA issued a final report on its Software-as-Medical-Device (SaMD) Pre-certification Pilot program in which the agency acknowledged the learnings and challenges identified by the Pilot.
- "From real-world data to real-world evidence: An interregional perspective" examines the application of real-world data for drug development and regulatory approvals and the use of real-world evidence for medical decision making. Frameworks for RWD and RWE are being developed by FDA.

U.S. Pharmacopeia (USP)

- USP PF 48(1) published a new revision of the chapter <1604> Presentation of the Aerodynamic Particle Size Distribution (APSD) Data for Orally Inhaled Drug Products.
- USP PF 48(1) included a Stimuli Article for public comment, Analytical Instrument and System Qualification to Support Analytical Procedure Validation over the Life Cycle.
- USP PharmForum 48(2) published revisions to a number of chapters, including the following:
  - Measurement Uncertainty Evaluation Relevant to Analytical Instrument and System (AIS) Qualification - The Role of Measurement Uncertainty Concepts within the AIS.
  - Sterility by Design for Sterile Drug Products.
  - Refining Microbiological Control and Testing for Nonsterile Products.
  - Fluticasone Propionate Inhalation Aerosol.
  - Fluticasone Propionate Inhalation Powder.
  - Fluticasone Propionate and Salmeterol Inhalation Aerosol.
  - Fluticasone Propionate and Salmeterol Inhalation Powder.
  - Salmeterol Inhalation Powder.
- USP PharmForum 48(3) published several stimuli articles and new or revised chapters for comment, including:
  - <1236> SOLUBILITY MEASUREMENTS.
  - Overview of the Activities of the USP Expert Panel on New Advancements in Product Performance Testing.
  - USP's Iterative Approach to Standards Development and the "Emerging Standards" Concept.
  - In Vitro Performance Tests for Continuous Manufacturing: The Impact on the Current Compendial Framework from the Viewpoint of the USP New Advancements in Product Performance Testing Expert Panel [PF48(4)].
  - Pharmacopeial Forum Introduction [PF48(4)].

- (1078) Good Manufacturing Practices for Bulk Pharmaceutical Excipients [PF48(4)].
- (1079.3) Monitoring Devices - Time, Temperature, and Humidity and (1118) Monitoring Devices - Time, Temperature, and Humidity [PF48(4)].
- (1094) Capsules - Dissolution Testing and Related Quality Attributes [PF48(4)].
- (601) inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders - Performance Quality Tests [PF48(4)].

- USP PharmForum #48(6) (64) opened a number of new and revised chapters for comment including the following:
  - (232) Elemental Impurities—Limits.
  - (604) Leak Rate (Of Aerosol Containers).
  - (711) Dissolution.
  - (1033) Biological Assay Validation (E.G., For Vaccines).
  - (1153) Drug Products Containing Nanomaterials (Including Those For Inhalation).
  - (1154) Liposome Drug Products (Including those for inhalation).

U.S. National Institutes of Health (NIH)

- The US National Institutes of Health (NIH) will start requiring data sharing plans in grant applications in January 2023.

U.S. Environmental Protection Agency (EPA)

- The US Environmental Protection Agency (EPA) Administrator signed the proposed rule, Phasedown of Hydrofluorocarbons: Restrictions on Certain Uses of Hydrofluorocarbons Under Subsection (i) of the American Innovation and Manufacturing Act.

Association for the Advancement of Medical Instrumentation (AAMI)

- AAMI revised an American National Standard as guideline, AAMI HE75, Human factors engineering—Design of medical devices.

II. Events, Webinars, & Meetings

- FDA and CERSI conducted a series of free online webinars about cybersecurity.
- FDA Webinar on Draft Guidances on Transition Plans for COVID-19 Related Medical Devices (February 22, 2022).
- FDA, the UK Medicines and Healthcare products Regulatory Agency (MHRA), and Health Canada GCP Workshop "Global Clinical Trials - Considerations and Lessons Learned from the Changing Landscape" (March 7-9, 2022).
- FDA-EMA Parallel Scientific Advice (PSA) Program Webinar (March 16, 2022) Recording can be found on the FDA SBIA YouTube Channel.
- Generics Drug Forum – FDA Webcast (April 26-27, 2022).
- PQRI Workshop: Managing Excipient and API Impact on Continuous Manufacturing (May 17-18, 2022).
- US-Canada ICH Consultation Public Meeting (May 11, 2022).
- FDA Workshops:
  - FDA Generic Drug Science and Research Initiatives Public Workshop (May 9-10, 2022).
  - FDA Workshop on Quality Management Maturity (May 24-25, 2022).
  - Building Medical Device Supply Chain Resilience: A Healthcare and Public Health Ecosystem-Wide Collaboration (June 7-9, 2022).
  - IVIVC and in-vitro release tests for ophthalmic, injectable, implantable and insertable products (June 29, 2022).
  - Patient Focused Drug Development: Tools for Use in Clinical Trials (June 30, 2022; July 25, 2022).
  - Advancing Generic Drug Development: Translating Science to Approval (September 20-21, 2022).
  - Nanomaterials, including liposomes and lipid nanoparticles (October 11, 2022).
- AAMI/FDA/BSI International Standards Conference 2022 (October 18-19, 2022).
- FDA NanoDay Symposium (October 11, 2022): Discussed the final CMC guidance "Drug Products, Including Biological Products, that Contain Nanomaterials - Guidance for Industry," mRNAs vaccines case studies, FDA's participation in the development of standards for nanomaterials, continuous manufacturing involving nanomaterials, liposomal lipid quantitation, other considerations for liposomes and lipid nanoparticles. Full agenda can be found here.
- FDA Webinar: Offered an overview of the finalized guidance entitled Clinical Decision Support (CDS) Software (October 18, 2022). The webinar slides and other details are available here.
- FDA/PQRI Workshop: Regulatory Framework for Distributed and Point of Care Pharmaceutical Manufacturing: An Opportunity for DM/POC Stakeholder Engagement (November 14-16, 2022).
- CRCG/FDA Workshop: Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned (December 6, 2022).

Questions?

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