IPQ
INTERNATIONAL PHARMACEUTICAL QUALITY
Inside the Global Regulatory Dialogue

CURRENT INSIGHTS FROM LEADING REGULATORS

African Medicines Agency Will Play Key Role in Continental Regulatory Ecosystem Alongside Regional Initiatives and National Authorities

At the DIA Europe Conference, held in Brussels in mid-March, African Medicines Regulatory Harmonization (AMRH) Initiative Head Chimwemwe Chamdimba discussed: • the background of the African Medicines Agency and the foundational role of the AMRH • AMA key functions and current status • ongoing AMRH technical support to the AMA • continental processes, standards and guidelines, and • reliance and regulatory system strengthening.

UPDATES IN BRIEF: GLOBAL CMC/GMP DEVELOPMENTS

• BARDA Launches Next Generation of the Accelerator Network • CDER's New Quantitative Medicine Center of Excellence • EDQM Seeking Feedback on HTS for the Detection of Viral Extraneous Agents • EDQM April Inspection, Certification and Reference Standard Activities • Malaysia NPRA's Revision of Timelines for Variation Applications of Registered Products • CBER Human Cells, Tissues, and Cellular and Tissue-Based Products Inspection Information • Senate Subcommittee Hearing on FDA's 2025 Budget Request • USP Notice of Intent to Omit Norflurane Monograph

FDA DRUG GMP WARNING LETTERS

Company	Facility Location	Product Type
Global Cosmetics	China	Finished

EMA GMP NON-COMPLIANCE REPORTS

Company	Facility Location	Product Type
Akriti	India	Finished

FDA DRUG RECALLS

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

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.

The African Medicines Agency to Play Key Role in Continental 'Regulatory Ecosystem' Alongside Regional Initiatives and National Authorities

The African Medicines Agency (AMA), now coming into operation, will be part of a continental regulatory ecosystem, relying heavily on the support and shared expertise of the five Regional Economic Communities (RECs) and the national authorities (NRAs).

At an "Africa Townhall" session focused on operationalization of the AMA at the DIA Europe Conference held in Brussels in mid-March, African Medicines Regulatory Harmonization (AMRH) Head Chimwemwe Chamdimba emphasized the role of the regional organizations and their ongoing initiatives, including Regional Centers of Regulatory Excellence (RCoREs).

"AMA is not the only solution to our regulatory challenges," she commented. "We will require AMA, RECs, and NRAs – each one of them playing their important role in the ecosystem, making sure that it is gelled and they are able to rely on each other." ***[Chamdimba's full remarks are appended below.]***

Regulatory capacity strengthening is another important facet of the AMA plans. Chamdimba noted that utilizing the other structures that are set up and partnering with key stakeholders "will continue to be our priority" to deliver on the AMA mandate, "as well as the issue of digitalization."

Among the platforms that have been created is a continental network of National Quality Control Laboratories. "We defined its work last year, and we want to make it functional this year," she said.

These laboratories are part of a "continental reliance framework," Chamdimba noted, that "we are going to use as a tool to support countries" in developing their reliance systems. In turn, "we will continue strengthening RECs, because they are an important component of our regulatory ecosystem."

The Africa Townhall session was co-moderated by EMA International Affairs Head Martin Harvey Allchurch and International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Regulatory Affairs Associate Director Sarah Adam, who both provided introductory comments.

Leaders who have been heavily engaged in helping frame AMA through supporting organizations and agencies participated in a panel discussion following Chamdimba's presentation.

[Editor's Note: An upcoming in-depth story on the development of the African Medicines Agency, including the support the initiative has received from EMA and the Gates Foundation, will include the introductory comments and the panel discussion.]

Need for AMA Recognized in 2005

Chamdimba began her remarks by providing background to the development of the African Medicines Agency – going back to 2005 when the Heads of States adopted the Pharmaceutical Manufacturing Plan for Africa (PMPA).

She then explained how the African Medicines Regulatory Harmonization initiative was established and was the "foundation" of the AMA. The aim of the AMRH was to improve regulatory capacity and provide an "enabling environment" for R&D and local production of pharmaceutical products that "meet internationally acceptable standards of quality, safety, and efficacy."

Considering the size of the continent, with its 55 countries and five economic regions, a stepwise approach to harmonization is necessary, Chamdimba explained. The five regions are the: ● East African Community (EAC) ● South African Development Community (SADC) ● Economic Community of West African States (ECOWAS) ● Economic Community of Central African States (ECCAS), and ● Inter-Governmental Authority on Development (IGAD) in East Africa.

Moving on to discuss the AMA's functions and progress, Chamdimba pointed out that, "importantly," the agency will provide "regulatory guidance, scientific opinion, and a common framework for regulatory actions on medical products" across the continent.

"That is at the core of it," she said, emphasizing that the AMA is "not going to replace the national regulatory authorities or take over the regulation of all products that are going to be going into the African continent."

Instead, AMA will deal with a "specific group of medical products, which the countries are not able to deal with on their own, which are the complex molecules." And there will be a need to "mobilize ambassadors from across the continent to be able to jointly work together, to rely on each other, and collectively move" when bringing these products to the African market.

AMA Establishment is Progressing

Chamdimba then reviewed the progress being made in establishing the agency.

The AMA treaty came into force in 2021 and 26 countries had ratified the treaty as of the time of her presentation. A governance structure has been put in place and Rwanda has been chosen as the host country. Ongoing is the process of recruiting a Directorate General and Board of Directors. Ghana currently holds the position of Chair of the Bureau of the AMA.

Since Chamdimba's presentation, additional countries have ratified, including Ethiopia and Côte d'Ivoire. Of the five WHO "maturity level 3" benchmarked agencies in Africa, two have completed the ratification process – Egypt and Ghana. The other ML3 countries – Tanzania, South Africa, and Nigeria – are at different stages in their progress to ratification.

Encouraging the completion of the ratification process are industry and non-profit organizations, such as PATH, which has been actively involved in providing technical support to the process. A recent policy and advocacy article by PATH sets out ● its advocacy for ratification ● common roadblocks, and ● its role in supporting the ratification process. ***[A link to the PATH article is provided below.]***

The AMRH is providing ongoing support to the set-up of the African Medicines Agency through ten technical committees (TCs), including an African Medicines Quality Forum (AMQF), an Evaluation of Medicinal Products TC, and a GMP Inspections TC. The eight RCoREs, Chamdimba explained, "have been providing sustainable capacity strengthening for our regulators on the continent."

Continental Pilot Listing of Products Begins

An important area of work, Chamdimba stressed, is the establishment of continental processes, standards, and guidelines, which are "at par with international best practices." Critical to that is the involvement of ML3 member states and collaboration with EMA and other agencies "to be able to benchmark."

A "continental pilot listing of medicinal products" has begun, following a call for applications in November 2023. The pilot is led by the Evaluation of Medicinal Products and GMP TCs and is in collaboration with WHO, EMA, USFDA, BfArM, and Swissmedic – regulatory agencies that became recognized as WHO Listed Authorities (WLAs) in May.

> ***[Editor's Note: See IPQ's Weekly Supplement for the week ending April 19, 2024 for a discussion at the DIA Europe WHO Townhall session of how WHO is transitioning from its previous "Stringent Regulatory Authority" classification system to WLAs. A link to the May WHO release announcing the second round of WLA approvals is provided below.]***

Pointing to a number of key documents and processes developed by the EMP and GMP TCs, Chamdimba reached out to stakeholders for their input. "We are open to your comments and your input whenever you think that we should consider certain things that we have not done."

> **She recognized the contribution that IFPMA, EMA, the Gates Foundation, in particular, have been making in supporting the guidelines, standards, and processes on which the pilot rests.**

In her closing remarks, Chamdimba stressed the need for continental reliance, because "we know we can do all this continental work, we can do all these processes at the continent or regional level, but if the countries do not have systems for reliance, it will be very difficult for them to implement anything that we will decide on at a continental level."

LINKS:

- AUDA-NEPAD AMRH Website
- PATH Article on Ratifying the AMA Treaty
- WHO May Release on Approval of WLAs
- AMRH Resources

[Subscribers CLICK HERE for Chamdimba's complete remarks at the DIA 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**