Advancing Toward Harmonized Global Scientific and Technical Standards for Generic D*rugs*

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The Importance of Global Harmonization Efforts
Oct 2, 2023

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Outline

- Overview of OGD Global Affairs Program
- Highlights of Three Global Initiatives and Efforts
  - Generic Drug Cluster
  - FDA's ICH Efforts Related to Generic Drug Harmonization
  - FDA-EMA Parallel Scientific Advice Pilot Program
- Take Home Messages

Overview of OGD Global Affairs Program
&
Generic Drug Cluster

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Generic Drug Global Affairs Program

Strengthen the FDA's global collaboration

Communicate effectively with stakeholders

Identify opportunities for early regulatory alignments

Engage proactively with regulatory counterparts

OGD GLOBAL AFFAIRS INTERNATIONAL EFFORTS

- Generic Drug Cluster fostering critical global partnerships
- Building partnerships to address global challenges and opportunities
- Efficiency in the harmonization process
- Establishing targeted outreach to support FDA regulatory needs
- Regulatory strengthening and capacity building of regulatory systems

REGULATORY HARMONIZATION

- Reducing duplication and inefficiency
- Improving quality and safety
- Facilitating access to medicines
- Enhanced transparency and traceability
- Improving clinical study standards

Generic Drug Global Engagement
Generic Drug Cluster

Global Generic Drug Affairs | FDA

GLOBAL RESPONSE

Monitor and analyze	Monitor and analyze the emerging trends and developments in the global arena that may affect the regulatory agency and its policies.
Review	Review the existing policies or new policies to address the gaps, challenges, opportunities, and risks posed by the global changes and policies.
Assess	Assess the impacts and implications of the global changes and policies on the regulatory agency and its policies. This may involve scenario analysis, risk assessment.
Evaluate and report	Evaluate and report on the performance and outcomes of the policies in relation to the goals and objectives of the regulatory agency and the global changes and policies.

GENERIC DRUG CLUSTER

https://www.fda.gov/drugs/generic-drugs/global-generic-drug-affairs

Approvability /Current review challenges

Regulations and guidances under development

Data integrity and information sharing

Data where regulatory requirements vary

Generic drug pipeline challenges

Accessibility challenges due to emerging global regulatory challenges

CLUSTER TOPIC EXAMPLES TO DATE

- Evaluating the active pharmaceutical ingredient sameness, particularly the peptide functionality/activities, using in vitro and in vivo assays
- Complex products with no generic competition
- Understand other generic cluster member agencies' approval standards, rationales behind, and review experiences, specifically pAUC recommendation for this product
- Presentation on member agency use of foreign comparator
- Comparison of narrow therapeutic index (NTI) classification and NTI bioequivalence (BE) approach among different agencies
- Discussed the challenges with assessing the data from Alcohol Dose Dumping studies
- Safety data of BE studies conducted in healthy subjects vs patient population (complex product where BE subject variation exists among agencies)
- Investigation on the pharmacokinetic profiles of parenteral nanotechnology products

FDA's ICH Efforts Related to Generic Drug Harmonization

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Global Harmonization of BE Standards

- Recommended topics for harmonization
- Recommended an order for prioritization

ICH M13: Bioequivalence for immediate-release (IR) solid oral dosage forms

www.ich.org

BE: Bioequivalence

M13 Guideline Series

HVD: highly variable drug; NTI: narrow therapeutic index

Progress Status of M13

M13A

- **Current Status:** Step 3 Regulatory consultation and discussion

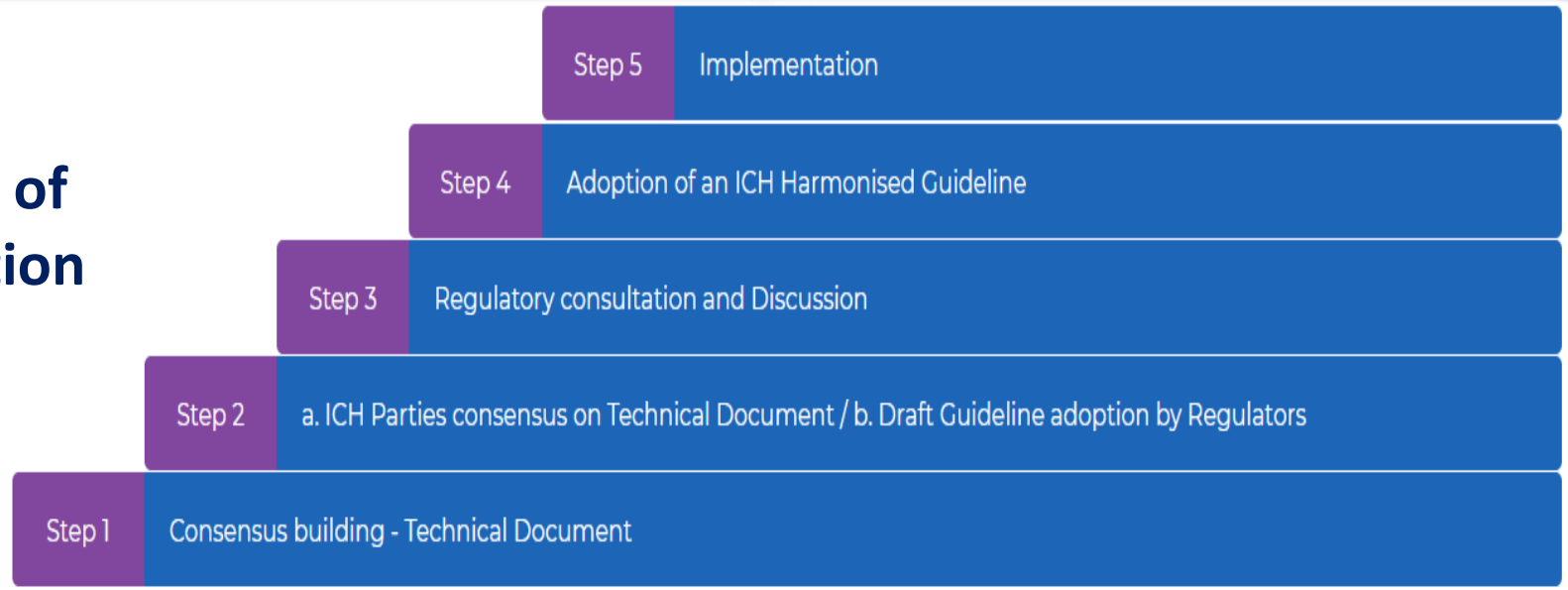
M13B

- **Current Status:** Step 1 Draft technical document under development towards consensus

M13C

- Start: After M13B *Step 2*

ICH Process of Harmonization



Notable Feature of Draft M13A

Reduced number of in-vivo BE studies

Testing under fasting condition for majority of drugs	BE may be demonstrated in a single study conducted under fasting conditions, except for high-risk products
Multiple comparator and multiple test products	E.g., 3-way crossover study with: - 2 comparator products from different regions against a single test product or - multiple test formulations against a single comparator product
Alternate approach with adequate justification	Deviations may be acceptable if appropriate scientific justification is provided. Applicants are encouraged to consult the regulatory authority(ies) when an alternate approach is proposed or taken

Next New Guideline Sponsored by ICH GDG Parties

ICH GDG (2020-2021)

- Year 2: Continued sharing information on multiple complex products and prioritizing the topics for harmonization
- Submitted a joint proposal to develop a guideline for MR products (including oral MR dosage forms)

  Potential to incorporate TDDS and LAI as series or annexes in the guideline

ICH Assembly - 2023

- Endorsed “BE for oral modified-release products” as the next ICH Guideline (June 2023)
- Start time is contingent on progress of M13

MR: Modified-Release; TDDS: Transdermal Drug Delivery System; LAI: Long-Acting Injectables

FDA-EMA Parallel Scientific Advice Pilot Program

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Parallel Scientific Advice (PSA) Program

Launched on **September 15, 2021**

The **Parallel Scientific Advice (PSA)** pilot program between FDA and European Medicines Agency (EMA) established a new PSA process for ***complex* generic drugs (FDA)/hybrid products (EMA)**

- An expansion to the existing PSA programs for new drugs (CDER) and vaccines or gene therapies (CBER)

The PSA pilot program allows for applicants to engage in **concurrent scientific conversation** with both agencies on key issues during the development phase of ***complex generic drug products and hybrid products***

PSA General Principles document

Why PSA?

Increases dialogue between the two agencies

Optimizes the applicant's global product development program by enabling them to discuss specific questions concurrently with both agencies

Further provides applicants with a deeper understanding of the basis for regulatory decisions from both agencies

Drives convergency to help applicants avoid redundant replication of work and unnecessary testing replication or unnecessary diverse testing methodologies

Shortens the time to drug development and approval

Comparison Between PSA and PDEV Meetings

	Parallel Scientific Advice (PSA)	Product Development (PDEV)
Eligible Products	Complex/Hybrid Products*	Complex**
When to Request a Meeting	Seek advice from both FDA and EMA on a global development program	Generally, no PSG, or new alternative BE methods different from PSG recommendation
How to Request a Meeting	A single request to two email boxes: emainternational@ema.europa.eu (EMA) and preANDAHelp@fda.hhs.gov (FDA)	Send request through NexGen Portal
Grant/Deny Decision Timeline	14 days to determine if accept full package	14 days
Days to Conduct Meeting	~120 days from receiving the full package***	120 days from meeting being granted
Participants at the Meeting	FDA, EMA and Applicant	FDA and Applicant
Format of the Meeting	Teleconference with video option (Videoconference)	In Person face-to-face or videoconference
Meeting Length	90 min	60 min

*Some complex products under U.S. FDA definition may be generic products under EMA. These products may also be eligible for PSA

** A PDEV meeting may be granted for a non-complex generic product

***The time between meeting request is accepted and full package submission could vary

What Have We Learned? (1)

The number of applicants who submit generic drug applications to the FDA and the centralized EMA process is limited

- Two PSA meeting requests were granted and have gone through the PSA process
- The PSA program can be an opportunity to expand the number of generic drug applicants that do submit applications to both jurisdictions

Some applicants have expressed concerns that the PSA program would require additional testing beyond what would be expected if the applicant sought individual advice from each regulatory agency

- However, that has not been the experience with the pilot applications

A learning experience for both regulators and applicants

- Understand differences in process and meeting expectation
- Converge on Science

What ave We Learned? (2)

In general, the pilot was implemented as intended, demonstrating long-term potential

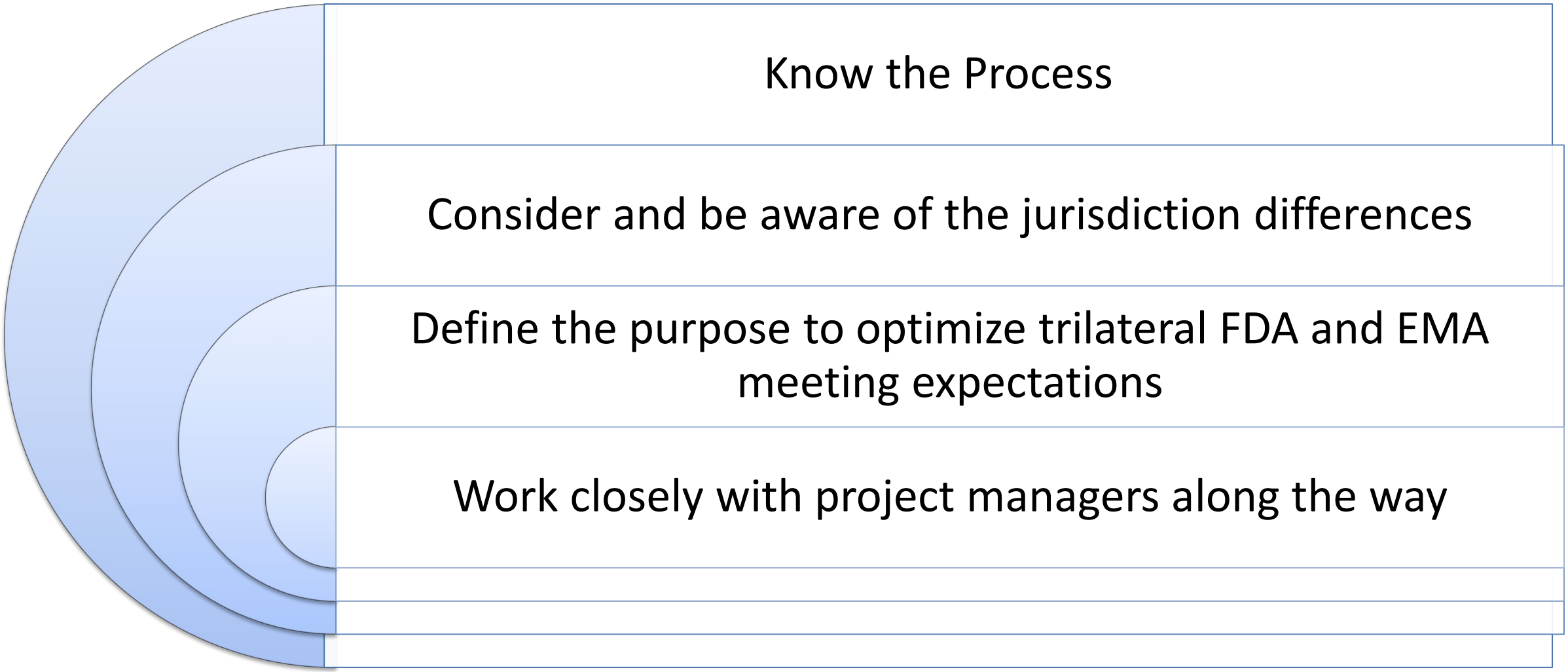
- Immediate benefits were more visible to regulators than applicants
- The designed process can be clarified and further improved

Recommendations were made based on program's preliminary assessment

- Procedural clarifications
- Clarity of the timeline and expectations
- Best practices for meeting package preparation and participation

FDA has communicated with EMA and implemented key recommendations to further improve the process

Tips for Participation



Take Home Messages

- FDA is committed to taking steps to enhance and streamline the development and approvals of high-quality generic drugs
  - Collaborate and share information via generic drug cluster
  - Promote harmonization of BE standards
  - Reduce redundancy and promote efficient drug development via parallel scientific advice

- FDA highly encourages applicants to participate
  - ICH harmonization efforts as equal contributor
  - PSA on complex/hybrid drug products

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