Global Regulatory Harmonization Challenges and Opportunities: FDA Perspective

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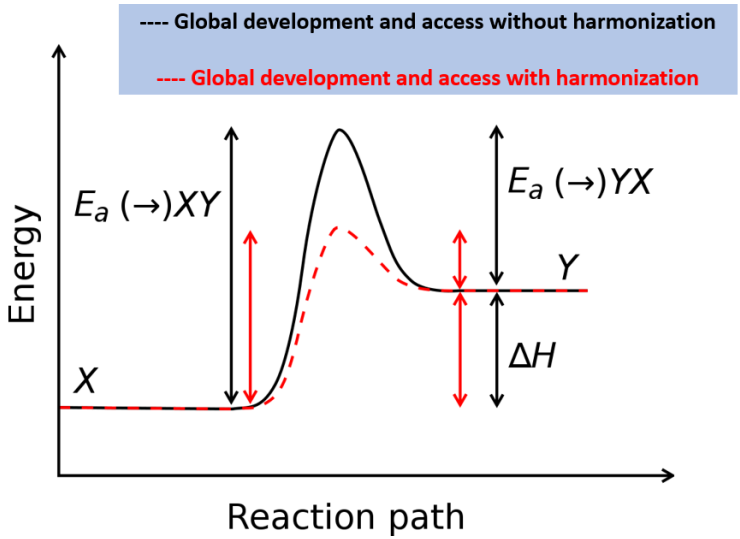
What is Pharmaceutical Quality?

- A quality product of any kind consistently meets the expectations of the user
  - Drugs are no different
- Patients expect safe and effective medicine with every dose they take
- Pharmaceutical quality is assuring every dose is safe and effective, free of contamination and defects
  - It is what gives patients confidence in their next dose of medicine




Global Harmonization

- FDA is one of many global regulators.
- Therapies are increasingly made available to multiple regions.
- Recognition that differences in regulatory systems should not hinder development or access to therapies.
- Global harmonization can be a catalyst to facilitate development and availability of therapies.



Global Harmonization

- Multiple forums for global harmonization each with a specific niche.

- For example:
  - International Council on Harmonisation (ICH) – Guidelines for scientific and technical aspects of pharmaceuticals.
  - International Coalition of Medicines Regulatory Authorities (ICRMA) - executive-level, strategic coordinating, advocacy and leadership.
  - Pharmaceutical Inspection Co-operation Scheme (PIC/S) - international development of harmonized GMP standards and quality systems of Inspectorates.

International Council for Harmonisation

- Focus on harmonizing scientific and technical requirements for human pharmaceuticals through technical guidelines.
- Key areas include quality, safety, efficacy, and multidisciplinary guidelines.
- 20 Members and 35 Observers
- Global harmonization must accommodate many regulators, and a variety of legal frameworks and scientific positions.

ICH Quality Guidelines Currently in Development

- ICH Q2(R2)/Q14 Analytical Procedure Development and Validation
- ICH Q3E Impurity: Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics
- ICH Q5A(R2) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
- ICH Q9(R1) Quality Risk Management
- ICH Q13 Continuous Manufacturing
- M4Q(R2) CTD on Quality

Perspectives on Success Factors for Global Harmonization

1. Experience:
   - Clarity in regional policy position.
   - Regulators and industry have perspectives informed by experience.

2. Buy in:
   - Shared technical and regulatory problem across multiple regions.
   - Shared improvement for both regulator and industry.

3. Implementable solutions:
   - Ideally, minimal need to change legal frameworks (e.g. statute and regulation).
   - Regulators and Industry have sufficient capabilities to implement.

Experience

- Experience on the topic from parties at the table drives robust debate and stronger solutions:
  - Allows for parties to develop clear positions before and during negotiation.
  - Identify where existing tools can help address the concern, or where new tools are needed.
  - Identify modification or elaboration to existing policy.

Experience

- ICH Q9(R1) example:
  - ~15 years of experience with the practical implementation of ICH Q9.
  - Saw room to clarify subjectivity in risk assessment, increase formality in QRM framework and decision making, and apply QRM to broader concepts like product availability.

- ICH Q7 Questions and Answers example:
  - Multiple interactions between regulator and industry regarding identification of regulatory starting material and resultant regulatory impact (e.g. data, CGMP).
  - Applying these examples to existing regulatory frameworks enabled parties to align on a Q&A position for regulatory starting material (and other Q&A) in less than 3 years.

Buy In

- Technical topic should be of interest to all parties:
  - Multinational topic where guideline could bring valuable clarity.
- Helpful to identify benefits for all parties, including those that are mutual.
- Can apply to both current issues and emerging topics:
  - Important to understand maturity of the issue to modulate the level of alignment and depth of solutions needed.

Buy In

- ICH Q12 example:
  - Mutual interest between regulator and industry to:
    - Enable enhanced scientific development and control approaches
    - Maximize agility of pharmaceutical industry
    - Reduce unnecessary regulatory oversight of CMC changes where science would allow for reduction in reporting.
  - Q12 maximized utility of existing tools and envisioned a science-based framework to reduce reportable changes.
  - Resulted in enhanced product knowledge, and increased agility for both regulators and industry.
  - Reduction in global change complexity facilitates changes to improve quality over lifecycle.

Buy In

- ICH Q13 example:
  - Alignment across regulators and industry that continuous manufacturing (CM) can improve product quality through more efficient and controlled manufacturing operations.
  - Development and adoption with industry has emerged in recent years.
  - Global guideline could broadly facilitate implementation, regulatory approval, and lifecycle management by addressing challenges caused by a lack of guidance.

Implementable Solutions

- Working within legal frameworks can:
  - Allow for scientific concepts to lead negotiations.
  - Provide necessary confidence for regulators and industry that a negotiated guideline can be feasibly implemented.
  - However, modifications to legal frameworks are possible.

Implementable Solutions

- ICH Q12 example:
  - Regulatory frameworks allowed for different levels CMC change reporting depending on its potential risk to product quality.
  - Allowed for negotiations to focus on how scientific (e.g., ICH Q8 and Q9) and control approaches (e.g. ICH Q10) enable use of regulatory tools (e.g., lifecycle management document, change management protocols).
  - Some regulators made / intend to make changes to legal frameworks to accommodate new regulatory tools (large buy-in from all parties).

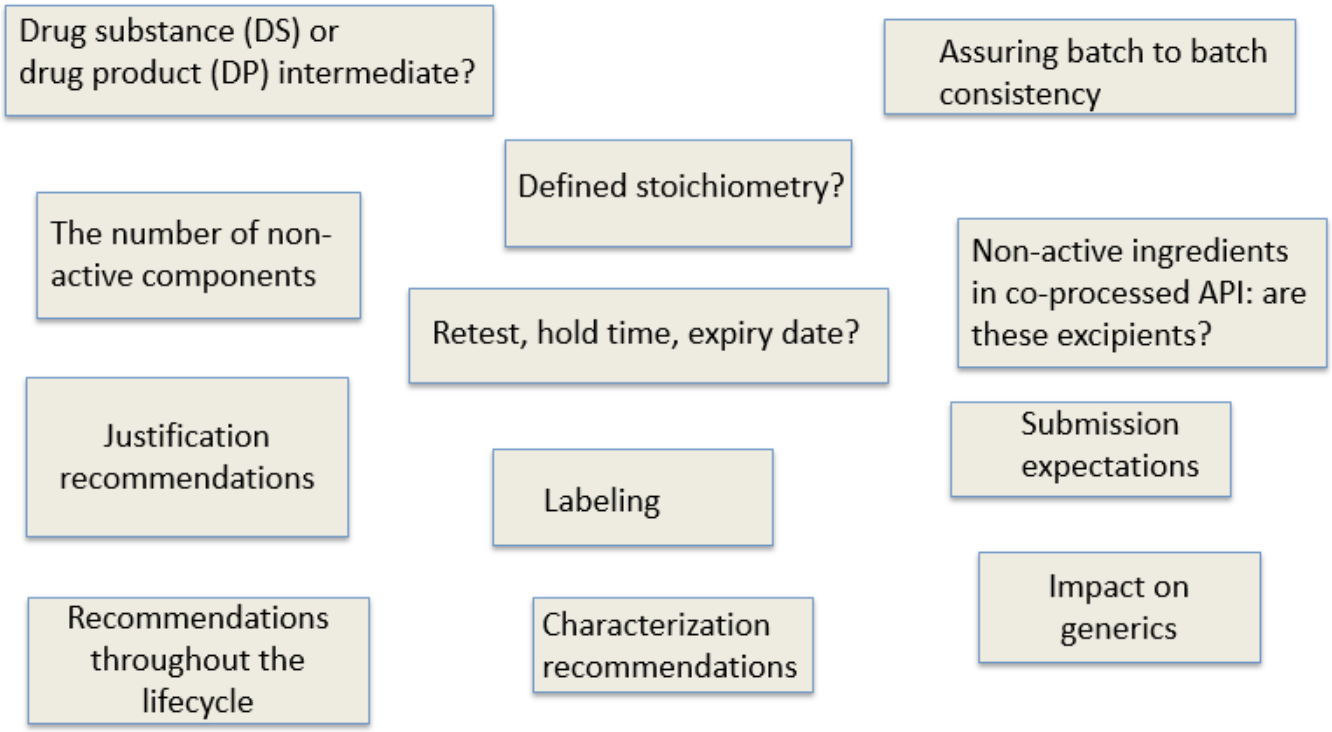
Relevance to Co-Processed API

- FDA's framework has definitions for API, Drug Substance, and Drug Product:
  - API: any component that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body.
  - Drug Substance: Active ingredient…does not include intermediates
  - Drug Product: finished dosage form that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients.

- Technical and regulatory frameworks influenced by this foundation, e.g.:
  - Current good manufacturing practice
  - Expiry vs retest, stability studies
  - Regulatory filings (DMF vs application)

Potential Challenges of Co-Processed APIs

- Many nuances that need to be explored within the current regulatory framework



- Laurie Graham, FDA/CDER/OPQ/OPPQ

Concluding Remarks

- We are at a starting point:
  - Crystallization around FDA approach:
    - What requires more clarity, or new / revised policy?
    - What aspects are sufficiently addressed by current regulatory framework?
  - Understanding global landscape:
    - To what extent is this a multinational issue?
    - How well do existing guidelines address the issue?
    - What tool(s) would best address nuances across regions?

Concluding Remarks

- Global harmonization takes time and effort.
  - Years to reach alignment and initial adoption
  - Additional time to realize implementation and culture change
  - Implementation experience drives revisions

- FDA/CDER supports innovation in technical and regulatory approaches that improve quality and availability of drugs.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