Policy Initiatives for Pharmaceutical Quality

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Learning Objectives

- Understand the scope of pharmaceutical quality policy
- Gain an appreciation for policy initiatives underway
- Understand how OPQ is involved in international harmonization

The Quality Landscape

OPQ is responsible for quality of:

- Innovator products
- Generics
- Biotechnology products
- Biosimilars
- OTC Monograph products
- 503B Outsourcing Facility products

Through:

- Application assessment
- Inspection outcomes (from preapproval, postapproval, surveillance, for-cause inspections)
- Surveillance activities
- Engagement with foreign regulators
- Research
- Answering inquiries from industry stakeholders

Quality Policy Activities in 2018

- Published **12 guidance documents**
- Published **7 MAPP documents**
- Responded to **554 controlled correspondence**
- Responded to **230 external inquiries**

Quality Guidances Published in 2018

FINAL	Regulatory Classification of Pharmaceutical Co-Crystals	2/14/18
FINAL	Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation	4/5/2018
REV DRAFT	Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products	4/19/18
DRAFT	Field Alert Report Submission	7/19/18
DRAFT	Use of Liquids and/or Soft-Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments	7/25/18
FINAL	Elemental Impurities in Drug Products	8/8/18
FINAL	Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances	8/9/18
FINAL	Quality Attribute Considerations for Chewable Tablets	8/21/18
DRAFT	Postapproval Changes to Drug Substance (GDUFA II)	9/11/18
FINAL	Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use	10/3/18
REV DRAFT	CGMP-Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B	12/11/18
DRAFT	Data Integrity and Compliance With Current Good Manufacturing Practice	12/13/18

Quality Guidances Published in 2019

DRAFT	CDER's Program for the Recognition of Voluntary Consensus Standards Related to Pharmaceutical Quality	2/14/2019
DRAFT	Quality Considerations for Continuous Manufacturing	2/27/2019
FINAL	Extending Expiration Dates of Doxycycline Tablets and Capsules in Strategic Stockpiles	4/24/2019
DRAFT	Using the Inactive Ingredient Database Guidance for Industry	7/10/2019
DRAFT	Harmonizing Compendial Standards With Drug Application Approval Using the USP Pending Monograph Process Guidance for Industry	7/10/2019

More to Come…

- FDA maintains a public guidance agenda
  - New and revised draft guidances CDER plans to publish during each calendar year
- For 2019, includes:
  - Drug Master Files; Revised Draft
  - Type V DMFs for CDER-Led Combination Products Using Device Constituent Parts with Electronics or Software
  - Risk Management Plans for Drug Manufacturers
  - Transdermal and Topical Delivery Systems - Product Development and Quality Considerations
  - Stability Considerations for NDAs, ANDAs and BLAs
  - ANDAs: Stability Testing of Drug Substances and Products Questions and Answers
  - Microbiological Considerations for Non-Sterile Drug Products
  - Quality Considerations for Topical Ophthalmic Drug Products
  - Inspection of Injectable Products for Visible Particulates

Policy Document Review

- Review of existing policy documents (150+ quality-related guidance documents)
  - Review of the policy and its documentation for relevance, effectiveness, and needed improvements
  - On a periodic basis, as proposed by internal staff, or resulting from stakeholder feedback
- Is a systematic approach to collect, analyze, and use information to evaluate whether a particular policy or related policies and the documents that articulate them (e.g., guidances, MAPPs, and compliance programs) are effective
- Can lead to improvements of the document's effectiveness by, for example, enhancing its quality through improving clarity of message, thereby helping industry and FDA staff to use their time and resources more effectively
- Can identify policy gaps, emergent risks, implementation failures, unintended consequences, inefficiencies, and other challenges

Selected Quality Initiatives

Expanding Use of Voluntary Consensus Standards

- Draft guidance proposing development of a CDER informal standards recognition program published February 2019
- Proposed benefits to FDA and Industry:
  - Provide industry with useful reference materials/guidance
  - Review effort can be more focused
- Promote transparency/accountability in the development of standards
- Complement OPQ's other policy development efforts

Proposed Approach for CDER

- Draft guidance contains details of the proposed program
  - Different from CDRH standards recognition program, which was created as a result of FDAMA of 1997
- Allow anyone (internal or external) to propose/submit a standard for recognition with relevant information
- Ability to informally recognize a standard in whole or in part
- CDER would develop a mechanism to review and publish 'Information Sheet' on website describing scope and other relevant information for each recognized standard
- Currently reviewing docket comments and revising the draft

Addressing Post-Approval CMC Changes

ICH Q12 – Technical and Regulatory Considerations For Pharmaceutical Product Lifecycle Management

- Developed out of recognition that lack of harmonized requirements for lifecycle management is a disincentive to manufacturers to make improvements to increase process robustness
  - One post-approval change can take 3-5 years to implement across all regions, resulting in additional costs and potential supply disruption due to need to maintain multiple inventories
- Intended to:*
  - Facilitate **risk-based regulatory oversight**
  - Support **continual improvement** and facilitate introduction of **innovation**
  - **Enhance use of regulatory tools for prospective change management…enabling strategic management of post-approval changes…**

* From ICH Q12 Concept Paper

ICH Q12 Opportunities

Tools in ICH Q12, such as Established Conditions (ECs), offer opportunities for industry to:

- Gain clarity regarding:
  - Which elements of the control strategy must be reported if changed
  - How much flexibility exists within an identified EC (e.g., if the EC is blend speed of 10-20 rpm, only changes to include speeds <10 rpm or >20 rpm need be reported)
  - How to report changes to ECs
- Use knowledge about the product and manufacturing process gained through development and commercial manufacturing experience to gain regulatory flexibility for managing post-approval changes

Maintaining an effective PQS, especially with respect to change management, will be key to successful use of these tools

ICH Q12 – Next Steps

- Draft published for public consultation in 2018
- Expect Step 3 Expert Sign-off in November 2019
  - Training materials being developed for industry and regulators across all regions
- Implementation by regulators to follow
  - Will be published as FDA final guidance
- FDA conducting in-house training of assessors and investigators; identifying implementation issues from ongoing Established Conditions pilot

Linking Quality to the Patient

- Manufacturers should pursue development of a patient-focused, risk-based, overall control strategy
- FDA **published a white paper** in Jan 2018 describing key considerations when creating a Quality Overall Summary (QOS) that should:
  - explain product and process development in a patient-focused context
  - effectively summarize the overall control strategy
  - guide the regulator through the submission
- In other words – an effective QOS accurately conveys the development story:

Exploring the Potential of the QOS

- FDA white paper invited applicants (NDAs, ANDAs, BLAs) to explore opportunities to improve the QOS
- An “improved” QOS should:
  - Be compliant with ICH M4Q
  - Conform to CTD expectations
  - Be supported by data cross-referenced to information in Module 3
- Regulator should be able to use the QOS to initiate the assessment of potential risk to the patient, and the control of such risk, in the commercially manufactured product.
- Could lead to a more effective and efficient quality assessment

FDA White Paper: A Regulatory Perspective on the Quality Overall Summary: Putting the Pieces Together, January 2018

Mature Quality Management through Strong Quality Metrics and Quality Culture Programs

- CDER first proposed a quality metrics program through draft guidance in 2015, revised draft guidance 2016
- Enhanced by data-driven, collaborative research with University of St. Gallen*
- Informed by experience shared by scientific organizations (e.g., ISPE, PDA), trade associations (e.g., PhRMA, PBOA, CHPA) and more recently by individual company experiences through the FDA quality metrics site visit program

- Quality metrics and quality culture programs are mutually beneficial to industry, the Agency, and patients, and therefore remain a key focus for FDA
- Part of an overall goal to encourage firms to shift from a focus on compliance with CGMPs to a focus on mature quality management
- *Stay tuned for more details this afternoon…*

*Reports can be obtained at: http://tectem.ch/institute/opex/fda

Seeking Harmonization

- Participation and leadership in ICH
  - Q12 “Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management”
  - Q13 “Continuous Manufacturing”
  - Q14 “Analytical Procedure Development” and Revision of Q2(R1) “Analytical Validation”
  - M9 “Biopharmaceutics Classification Based Biowaivers”
- Participation in PIC/S
  - Harmonizing inspections and sharing timely quality information (e.g., product quality defects, recalls)
  - FDA hosted PIC/S Annual Seminar in Chicago, September 2018

Seeking Harmonization, cont.

- Mutual Recognition Agreement (MRA) between FDA and the EU allows drug inspectors to rely upon information from inspections conducted within each others' borders
  - Agreement signed in November 2017
  - US assessment of EU member states completed July 2019
- From November 2017 – June 1, 2019:

	# Inspections
EU inspections conducted on behalf of FDA	54
FDA inspections conducted on behalf of EU	12
FDA inspections in the EU deferred	106

Conclusions

- Many quality initiatives with a focus on:
  - Linking quality to the patient
  - Encouraging continual improvement and innovation
  - Providing transparency into FDA's expectations
  - Seeking harmonization for regulatory efficiency

Challenge Question 1

True or False?

OPQ is responsible for the quality of drugs that don’t require an approved application.

Challenge 1 Answer

TRUE!

Challenge Question 2

Which initiative is intended to help applicants “tell the story” of their product and process development to the regulator?

A. Established Conditions
B. Quality Overall Summary (QOS)
C. Mutual Recognition Agreement

Challenge 2 Answer

B. Quality Overall Summary

Thank You!


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