U.S. FOOD & DRUG ADMINISTRATION

Pharmaceutical Quality Policy
What you need to know!

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Overview

- Types of policy documents
- FDA quality policy initiatives
- International harmonization efforts

Policy Documents

- Guidance
- Manual of Policies and Procedures (MAPPs)
- Compliance Programs (formerly Compliance Program Guidance Manual)

What is a Guidance Document?

- Guidance documents are documents prepared for FDA staff, applicants/ sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue.
- FDA's procedures for developing and publishing guidance are established in 21 CFR 10.115 – Good Guidance Practices
- An applicant may choose to use an approach other than the one set forth in a guidance document. However, the alternative approach must comply with the relevant statutes and regulations.
- Although guidance documents do not legally bind FDA, they represent the agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence.

Types of Guidance Documents

- **Level 1 guidances** set forth FDA's initial interpretations of new significant regulatory requirements, describe substantial changes in FDA's earlier interpretation or policy, and deal with complex scientific or highly controversial issues
  - Issued in draft with a period for public comment (usually 60-90 days)
  - Upon review of public comments, guidance may be reissued as a revised draft or issued as a final guidance
- **Level 2 guidances** usually address existing practices or minor changes in FDA's interpretation or policy and are implemented without prior public comment

Types of Guidance Documents (cont.)

- **Draft guidances** describe new or significantly changed policy, are published for public comment, and are not for implementation
- **Final guidances** incorporate public comments received after a draft or revised draft has been published, are considered FDA's current thinking, and are for implementation
- **Revised draft guidances** update a draft guidance and are published for public comment
- **Revised final guidances** update a final guidance

MAPPs

- Document and disseminate CDER policies and procedures
- Standard MAPP
  - has no termination date and is available to the public
  - establishes office policies and procedures to guide staff in the conduct of their work
- Interim MAPP
  - is canceled, converted, or transferred after 3 years from the posted date
  - are not available to the public because the content is temporary (e.g., used for training before it becomes a Standard MAPP, used to test a pilot program)
- Internal MAPP
  - has no termination date and is not available to the public because
    1. it contains internal information that, if publicized, could interfere with important CDER objectives such as enforcement proceedings or confidential investigations;
    2. is of little or no interest to the public; or
    3. includes internally accessible information (e.g., CDER links to travel forms, passport forms, and other administrative information), the publication of which could weaken the FDA firewall protections

From MAPP 4000.1 Rev. 5 *Developing and Issuing MAPPs for CDER*

Compliance Programs

- Provide instructions to FDA personnel for conducting activities to evaluate industry compliance with the Federal Food, Drug, and Cosmetic Act and other laws administered by FDA, for example:
  - Approaches to inspection – full, abbreviated
  - Inspection coverage
  - Regulatory/administrative strategy
- Are made available to the public (https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/compliance-program-guidance-manual-cpgm)
- Examples include:
  - 7346.832 Pre-Approval Inspections/Investigations
  - 7356.002 Drug Manufacturing Inspections (surveillance)
  - 7356.002A Sterile Drug Process Inspections
  - 7356.002F Active Pharmaceutical Ingredients

Quality Guidance Published in 2019

- Guidance (GUI) DRAFT – CDER's Program for the Recognition of Voluntary Consensus Standards, *Published 2/14/19*
- GUI DRAFT - Quality Considerations for Continuous Manufacturing (CM), *Published 2/27/19*
- GUI FINAL - Extending Expiration Dates of Doxycycline Tablets and Capsules in Strategic Stockpiles, *Published 4/25/19*
- GUI DRAFT - Using the Inactive Ingredient Database (DCAP), *Published 7/11/19*
- GUI DRAFT - Harmonizing Compendial Standards with drug application CMC approval requirements using the USP pending monograph process (DCAP), *Published 7/11/19*
- GUI- L2 Q&A's: Level 2 guidance Questions and Answers on Current Good Manufacturing Practices — Laboratory Controls, *Posted 8/12/19*

Quality Guidance Published in 2019 (cont.)

- GUI FINAL - Child-Resistant Packaging Statements in Drug Product Labeling, *Published 8/14/19*
- GUI REV DRAFT - Drug Master Files, *Published 10/12/19*
- GUI DRAFT - Type V DMFs for CDER-Led Combination Products Using Device Constituent Parts With Electronics or Software, *Published 10/29/19*
- GUI DRAFT - Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Q & A Guidance (Level 2 GUI), *Posted 10/22/19*
- GUI DRAFT - Transdermal and Topical Delivery Systems - Product Development and Quality Considerations (DCAP), *Published 11/21/19*

Focus 2020 – COVID-19

- Policy for the Temporary Use of Portable Cryogenic Containers Not in Compliance With 21 CFR 211.94(e)(1) For Oxygen and Nitrogen During the COVID-19 Public Health Emergency, *Published April 20, 2020*
- Temporary Policy on Repackaging or Combining Propofol Drug Products During the COVID-19 Public Health Emergency, *Published April 22, 2020*
- Temporary Policy for Manufacture of Alcohol for Incorporation Into Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19), *Published June 1, 2020 (rev 4)*
- Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19), *Published June 1, 2020 (rev 4)*
- Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency, *Published June 1, 2020 (rev 4)*
- Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing, *Published June 19, 2020*

Quality Guidance Likely to Publish in 2020

- GUI – Control of N-Nitrosamine Impurities in Drugs
- GUI Final – Expiration Dating of Unit-Dose Repackaged Solid Oral Dosage Form Drug Products
- GUI Final – Comparability Protocols for Post approval Changes to the CMC Information in an NDA, ANDA, or BLA
- GUI Final – Drug Products, Including Biological Products, that Contain Nanomaterials
- GUI Final – Field Alert Report Submission: Questions and Answers

What's Coming Next?

- FDA maintains a public guidance agenda outlining new and revised draft guidances CDER plans to publish during each calendar year
- For 2020, includes:
  - Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research
  - Risk Management Plans to Mitigate the Potential for Drug Shortages
  - ICH Q12, General Considerations for FDA Implementation
  - Microbiological Considerations for Non-Sterile Drug Products
  - ANDAs: Stability Testing of Drug Substances and Products Questions and Answers
  - Quality and Stability Testing of Drug Substances and Drug Products for NDAs, ANDAs, and BLAs and Associated Labeling Statements for Drug Products

What's Coming Next (cont.)?

- For 2020, includes:
  - Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations
  - Chemistry Manufacturing and Controls Considerations for Individualize Antisense Oligonucleotide (ASO) Therapies
  - The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls
  - Quality Considerations for Topical Ophthalmic Drug Products
  - Inspection of Injectable Products for Visible Particulates
  - Setting Endotoxin Limits During Development of Investigational Oncology Drugs and Biologics

Recent MAPPs and CPs

- MAPP NEW - Center for Drug Evaluation and Research Biopharmaceutics Council, 5017.4, *Posted 4/24/19 (effective 5/16/19)*
- Compliance Program - 7346.832 Pre-Approval Inspections, *Posted 8/13/19*

International Harmonization

- Provides opportunities to reduce regulatory burden and incentivize continual improvement and innovation

Recently finalized:

- ICH Q12 *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*

Under development:

- ICH Q13 *Continuous Manufacturing*
- ICH Q2(R2)/Q14 *Analytical Procedure Development and Validation*
- ICH Q3E *Impurity: Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics*

New work item to begin in 2020:

- ICH Q9(R1) *Quality Risk Management*

International Harmonization (cont.)

- Opportunities for further input to the ICH development process
  - Quality Discussion Group (QDG)
    - ICH Reflection Paper on Advancing Biopharmaceutical Quality Standards to Support Continual Improvement and Innovation in Manufacturing Technologies and Approaches (endorsed June 2018)
  - Informal Generics Discussion Group (IGDG)
    - ICH Reflection Paper on Further Opportunities for Harmonization of Standards for Generic Drugs (endorsed November 2018)
- PIC/S – Pharmaceutical Inspectorate Cooperation Scheme
  - Draft Recommendation "How to Evaluate/Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management"

ICH Q12

Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

- Guideline finalized by ICH in November 2019 (https://ich.org/page/quality-guidelines)
- ICH IWG developing training materials for assessors and inspectors in cooperation with PIC/S, for use in all regions
- Final guidance (FDA version) to publish this summer
- Implementation of the full Q12 guideline in the U.S. begins with publication
  - Scope includes innovators, generics, biosimilars, CDER- and CBER-led combination products
  - Can be used for new products and already marketed products
- FDA guidance on details of implementation in the U.S. in development

ICH Q12 (cont.)

- Includes tools and enablers to facilitate continual improvement and innovation in a proactive manner
  - Established Conditions
    - Offer an opportunity to gain clarity regarding:
      - Which elements of the control strategy must be reported if changed
      - Which elements can be managed under the Pharmaceutical Quality System without reporting
      - How much flexibility exists to make changes to an identified EC
      - How to report changes to ECs
    - Can provide additional regulatory flexibility in managing post-approval CMC changes globally
  - Post-approval Change Management Protocols
    - Also known as “comparability protocols”
  - Product Lifecycle Management Document
  - Structured Approaches for Frequent CMC Post-Approval Changes

Conclusions

- FDA develops policy documents for industry stakeholders as well as for internal staff
- CDER's public guidance agenda provides insight into new and revised guidance in development for the coming year
- Developing internationally harmonized guidance provides an important opportunity to reduce regulatory burden for industry and incentivize continual improvement and harmonization

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