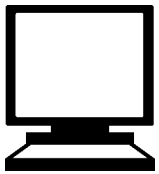
An FDA Perspective on Regulatory Considerations for Co-Processed Active Pharmaceutical Ingredients (APIs)

Laurie Graham-Eure
Director
Division of Internal Policies and Programs
Office of Policy for Pharmaceutical Quality
Office of Pharmaceutical Quality
CDER/FDA

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




Goal: To have discussions around the scientific and regulatory opportunities and challenges associated with co-processed APIs. My presentation will highlight some of the challenges, in the context of the existing regulatory and policy frameworks.

Outline

1. Potential Benefits
2. Potential Challenges
3. Underlying Regulatory Framework and Policies
   - Standards for different CDER regulated products
   - Current Good Manufacturing Practice (CGMP)
   - Control Strategy

Co-processed API (for purposes of this presentation)*: API plus one or more non-covalently bonded, nonactive component(s), and differs from salts, solvates and/or cocrystals

*Adapted from Schenck et al., Mol. Pharmaceutics 2020, 17, 2232−2244)

Potential Benefits of Co-Processed APIs

- Enhanced control of the physical properties of drug substances
- More robust and efficient manufacturing processes
  - Decreased cost and enhanced generic competition
- Improved product quality
- Innovation
  - Novel drug products
  - Advanced manufacturing (e.g., end to end continuous manufacturing)

Potential Challenges of Co-Processed APIs

Drug substance (DS) or drug product (DP) intermediate?

Assuring batch to batch consistency

Defined stoichiometry?

The number of non-active components

Non-active ingredients in co-processed API: are these excipients?

Retest, hold time, expiry date?

Justification recommendations

Submission expectations

Labeling

Impact on generics

Recommendations throughout the lifecycle

Characterization recommendations

Underlying Regulatory and Policy Framework

Statutory/Regulatory Expectations

- Drugs regulated under sections 505(b)(1), 505(b)(2), and 505(j) of the FD&C Act. Submission requirements are detailed in 21 CFR 314 and applicable guidance.
- Biological products regulated under section 351(a) and 351(k) of the PHS Act. Submission requirements are detailed in 21 CFR 601 and appliable guidance.
- Compounded products marketed by outsourcing facilities under section 503B of the FD&C Act.
- Nonapplication products (for example, OTC products marketed under the monograph construct (see 21 CFR 330.1 and 21 CFR Parts 331-358)).

Statutory/Regulatory Expectations

Cross-Referencing

- DMFs under 21 CFR 314.420 that are used to support new drug applications (NDAs), abbreviated new drug applications (ANDAs), and investigational new drug applications (INDs) under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

- DMFs and master files under 21 CFR 601.51(a) that are used to support biologics license applications (BLAs) under the Public Health Service Act (PHS Act).

Statutory/Regulatory Expectations

- Statutory and regulatory expectations for submission content and application approval remain the same, and will need to be met for applications proposing a co-processed API

Statutory/Regulatory Expectations

- Specific challenges for co-processed APIs will need to be addressed within these regulatory frameworks. For example
  - Where does information on the co-processed API get submitted in an application?
  - What information should be submitted to support a co-processed API?
  - Can an existing Type II DMF be updated to include co-processed API?

Impact on Each Regulatory Framework Example: Generics

- An ANDA is an application submitted and approved under section 505(j) of the FD&C Act for a drug product that is a duplicate of a previously approved drug product.
- An ANDA relies on FDA's finding that the previously approved drug product, i.e., the reference listed drug (RLD), is safe and effective.
- An ANDA generally must contain information to show that the proposed generic product

(1) is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and

(2) is bioequivalent to the RLD. An ANDA may not be submitted if clinical investigations are necessary to establish the safety and effectiveness of the proposed drug product.

Impact on Each Regulatory Framework Example: Generics

Need to consider the impact on different CDER regulatory pathways for co-processed APIs. For example, for generics, need to consider:

- Impact on API sameness
- Impact on Q1/Q2 assessments
- Changing to a co-processed API? What data would be needed?
- Implications of RLD labeling
- Exclusivity implications for RLD

Current Good Manufacturing Practice (CGMP)

CGMP

- CGMP provides for systems that assure proper design, monitoring, and control of manufacturing processes and facilities.
- Adherence to CGMP assures the identity, strength, quality, and purity of the drug by requiring that manufacturers of medications adequately control manufacturing operations.
- CGMP comprises minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product.

See Facts About the Current Good Manufacturing Practices (CGMPs) at https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps

CGMP: Regulatory Authority

- Section 501(a)(2)(B): “A drug... shall be deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.”

CGMP

APIs and drug products (DPs) are subject to the adulteration provisions of Section 501(a)(2)(B) of the Act, which requires all drugs to be manufactured in conformance with CGMP. No distinction is made between an API and a finished pharmaceutical in the Act and the failure of either to comply with CGMP constitutes a violation of the Act

See FDA Compliance Program 7356.002F for Active Pharmaceutical Ingredients

CGMP

While FDA has not promulgated CGMP regulations specifically for APIs or drug components (as we have for finished pharmaceuticals), FDA has long recognized that the CGMP requirements in the good manufacturing practice regulations for finished pharmaceuticals (21 CFR Parts 210 and 211) are valid and applicable in concept to active pharmaceutical ingredient (API) manufacturing. ICH Q7 represents the Food and Drug Administration's (FDA's) current thinking on CGMPs for APIs

See FDA Compliance Program 7356.002F for Active Pharmaceutical Ingredients

CGMP-process validation

Process validation is the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.

See FDA Guidance for Industry *Process Validation: General Principles and Practices*
https://www.fda.gov/files/drugs/published/Process-Validation--General-Principles-and-Practices.pdf

CGMP-process validation

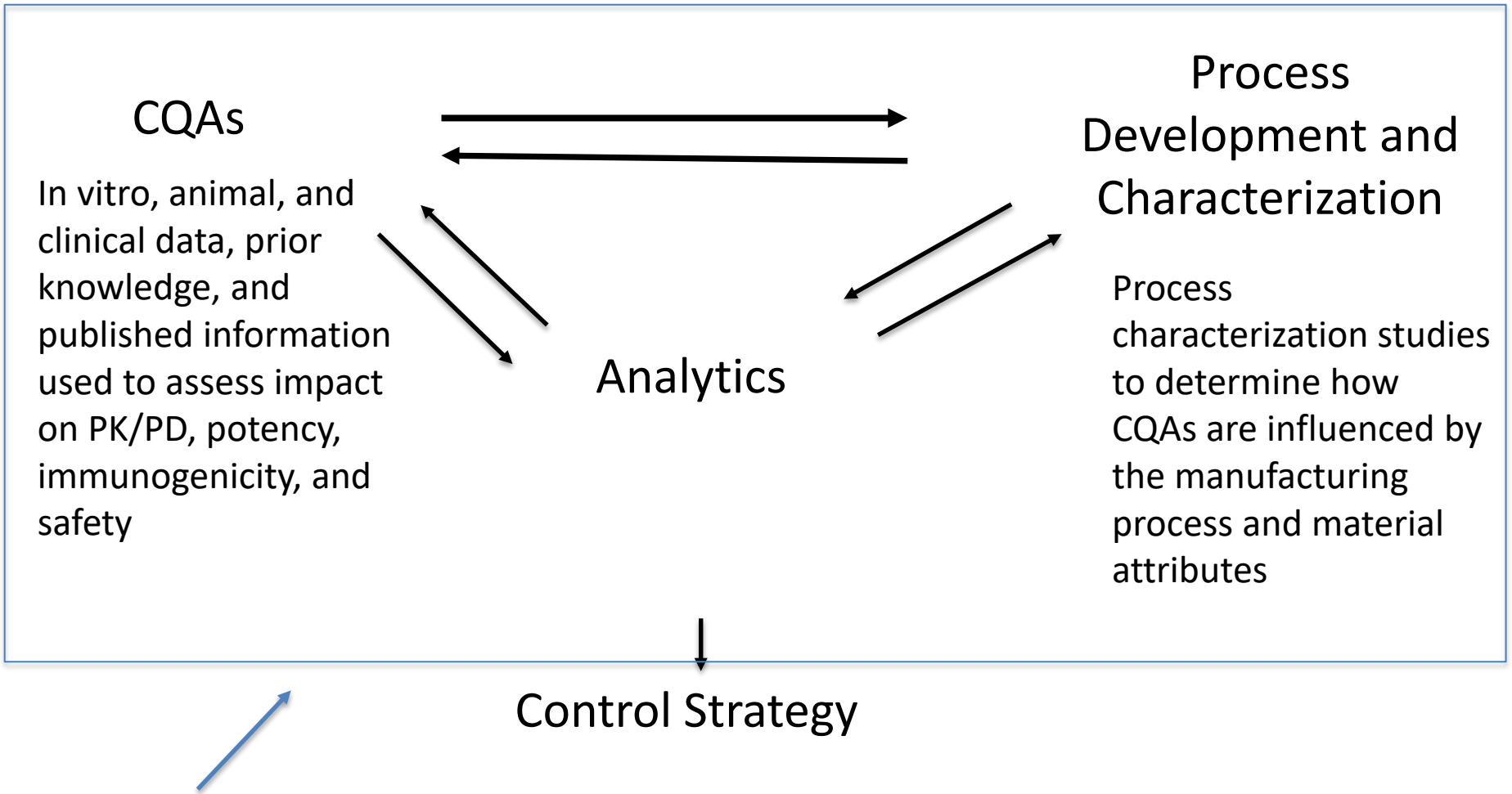
- Process validation for drugs is required to be successfully completed prior to commercial distribution under section 501(a)(2)(B) of the FD&C Act
  - methods and facilities used for the manufacturing of drugs be operated and administered under control sufficient to assure that the identity, strength, purity, and quality of a drug are as they purport or are represented to possess."
- APIs and components are subject to the statutory CGMP requirements of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 351(a)(2)(B)) and process validation is therefore required.

Facility Implications

- Regardless of whether co-processed API is manufactured in a DS facility or a DP facility, FDA's CGMP expectations and risk-based inspectional coverage will not change
- However, there are other factors to consider, such as:
  - Registration and listing implications
  - For generics, GDUFA facility fees for DS vs. DP facility

Control Strategy Development

Principles of Control Strategy Development



Control Strategy Development

- While the principles of control strategy development remain the same, what are the unique considerations for co-processed APIs?
  - Specifications: API and/or co-processed API?
  - Characterization recommendations
  - Stability expectations (e.g., is it a retest date, hold time, expiry date)
    - Need to support that storage under recommended conditions for the time indicated will not adversely impact product quality
- Consider different regulatory pathways. For generics
  - Comparative testing of generic product vs. RLD
  - USP monograph implications

Conclusion

- CDER is committed to supporting innovation and generic drug competition
- Innovation, such as through the use of co-processed APIs, has the potential to increase patient access to quality medicines
- Within the existing regulatory frameworks, there are unique challenges and gaps associated with co-processed APIs
- There are multiple factors that need to be considered in overcoming these challenges, including impact across CDER-regulated products


FDA
U.S. FOOD & DRUG
ADMINISTRATION