Requirements and Recommendations Related to Inactive Ingredients

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Excipients and Formulation Assessments of Complex Generic Products:
Best Practices and Lessons Learned
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Objectives

- Provide an overview of the regulatory framework around inactive ingredients for abbreviated new drug applications (ANDAs)

- Clarify the intersection between the requirements related to drug formulation and the requirements and recommendations for establishing bioequivalence (BE)

ANDA REGULATORY FRAMEWORK FOR INACTIVE INGREDIENTS

Section 505(j)(4)(H) of the FD&C Act

- Prohibits approval of an ANDA if
  - the inactive ingredients are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or
  - the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included is unsafe for use under such conditions.

Regulations on Inactive Ingredients

21 CFR 314.127(a)(8)(ii)(A)

- Permits FDA to deny approval of an ANDA if "there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety or efficacy."

- “FDA may identify changes in inactive ingredients or composition that may adversely affect a drug product's safety or efficacy" based on the Agency's "experience with reviewing inactive ingredients, and from other information available to it."

Regulations on Inactive Ingredients

21 CFR 314.94(a)(9)(iii) and (iv), and 314.127(a)(8)(ii)(B) and (C)

- FDA will consider an inactive ingredient in, or the composition of, a generic drug product intended for parenteral, ophthalmic, or otic use to be *unsafe* unless it contains the same inactive ingredients (with certain listed exceptions) in the same concentration as the ***RLD***.
  - Same inactive ingredients (qualitative sameness, Q1)
  - Same concentration (quantitative sameness, Q2)
  - Any differences in exception excipients must not impact the safety or efficacy of the drug product

Regulations on Inactive Ingredients

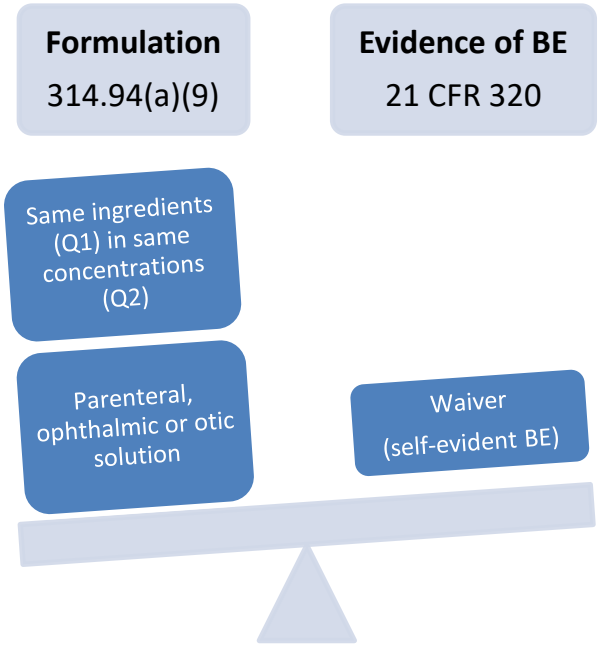
21 CFR 314.94(a)(9)(ii) and (v)

- Other types of drug products are permitted to contain different inactive ingredients in the formulation so long as any differences do not impact the safety and efficacy of the drug product

INTERSECTION OF FORMULATION AND ESTABLISHING BE

Formulation Sameness & Establishing BE

- Q1/Q2 sameness can impact what data are appropriate to demonstrate BE
  - For parenteral, ophthalmic, and otic solutions, Q1/Q2 same formulation can be expected to have same performance → BE self-evident
  - Where formulations are more complex (e.g., suspensions, emulsions), Q1/Q2 same formulation and acceptable comparative physicochemical characterization may be sufficient



Formulation Sameness

Required

- By regulation
- Drug product intended for:
  - Parenteral use
  - Ophthalmic use
  - Otic use

Recommended

- By guidance (including Product Specific Guidance (PSG))
  - Q1/Q2 sameness listed as criteria for using a particular BE approach
  - E.g., albuterol sulfate inhalation, timolol maleate ophthalmic, propofol injection

Establishing BE

- **21 CFR 320.21** requires submission of evidence of *in vivo* BE, unless an applicant can provide sufficient supporting information to permit FDA to waive the requirement

- **21 CFR 320.24** requires applicants to use the most accurate, sensitive, and reproducible approach capable of establishing BE for the drug product being tested
  - FDA's current thinking on what approaches would meet this requirement are reflected in PSGs

- **21 CFR 320.22(b)(1)** Biowaivers - requires Q1 and Q2 sameness in all inactive ingredients for BE to be considered "self evident"

Ophthalmic Drug Products

- Despite a similar allowance (to parenteral products) provided for ophthalmic drug products in 21 CFR 314.94(a)(9)(iv) for differences in exception excipients, an ANDA concerning an ophthalmic drug product should be **Q1 and Q2 the same as the RLD, including the exception excipients**, or include data from appropriate BE studies.

PSGs

- FDA's current thinking on the evidence needed to demonstrate that a generic drug is therapeutically equivalent to the reference listed drug (RLD) product.

- Assist the generic industry with identifying the most appropriate methodology and approaches for their generic drug development programs, including *in vivo* and/or *in vitro* BE studies, various waiver options (such as Biopharmaceutics Classification System (BCS)-based waiver), and dissolution testing methods.

Q1/Q2 Sameness in PSGs

- Criteria to use an in vitro approach
- PSGs describe FDA recommendations
  - Applicants are not required to follow PSG recommendations, but would need to justify that their alternative approach meets the statutory and regulatory requirements.

Q1/Q2 Sameness vs. “No Difference”

- For **topical drug products**, PSGs may include “no difference” criteria –
  - A demonstration that there are *no differences in the inactive ingredients or other aspects of the formulation* relative to the reference standard that may *significantly affect* systemic or local availability of the active ingredient
- Includes but does not require Q1 and Q2 sameness
  - Certain differences in Q1 and/or Q2 may not preclude a demonstration of Q3 sameness where the differences would not be expected to significantly affect systemic or local availability
  - Some examples of such differences include: A test topical product that (1) contains a Q2 difference in the amount of a pH-adjusting agent (that is used to adjust the pH of the test product to be the same as that of the reference standard), (2) uses the same Q2 amounts (or ranges) of each of the same subcomponents of a preblended ingredient used in the reference standard, or (3) uses a different grade of the same inactive ingredient (Q1 difference) that is considered to have the same identity as the inactive ingredient used in the reference standard.

PSGs

- FDA issues new and revised PSGs in batches on a quarterly basis and as needed as stand-alone postings.

- Published PSGs are announced in the Federal Register and made available to the public via FDA's website found at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

- FDA also provides information on upcoming new and revised PSGs for all generic drug products on a quarterly basis at the following website: https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-generic-drug-product-development

What if there is no PSG?

- Encourage applicants to reach out to FDA to discuss BE approach in pre-ANDA meeting
  - See Manual of Policies and Procedures (MaPP) 5220.8 *Evaluating Requests for and Conducting Product Development and Pre-Submission Pre-ANDA Meetings*.
  - See also FDA's guidances for industry, *Controlled Correspondence Related to Generic Drug Development* (December 2020), and *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022), for additional information on how to obtain Agency feedback on the development of a specific drug product.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