Bioequivalence Regulations and Product-Specific Guidances

Dave Coppersmith, JD
Regulatory Counsel
Office of Generic Drug Policy
Office of Generic Drugs | CDER | U.S. FDA

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Learning Objectives

- Discuss bioequivalence (BE) regulatory requirements and how they relate to product-specific guidances (PSGs).
- Discuss the availability of alternative approaches to recommendations in PSGs.
- Describe in vivo and in vitro BE testing requirements and recommendations.
- Describe how FDA revises PSGs.

BE Regulatory Requirements

- Regulations, such as 21 CFR part 320, are requirements and are binding on the public and FDA.
- Abbreviated New Drug Application (ANDA) applicants must conduct BE testing using the most accurate, sensitive, and reproducible approach available among those set forth in 21 CFR 320.24(b).

BE Regulatory Requirements, cont.

- Different types of evidence may be used to establish BE, including in vivo or in vitro testing, or both. 21 CFR 320.24(b).
- FDA has the authority to use any other approach deemed adequate by FDA to establish BE. 21 CFR 320.24(b)(6).
- FDA has significant discretion in determining the appropriate BE method.

BE Regulatory Requirements and PSGs

- PSGs and general BE guidance provide FDA's current thinking on the methodology for developing generic drugs and generating evidence to support ANDA approval.
- Recommendations in PSGs reflect FDA's thinking on the most accurate, sensitive, and reproducible approach to BE testing, consistent with 21 CFR 320.24.
- No regulatory requirement for FDA to publish a PSG prior to ANDA receipt or approval.

Alternative Approaches to Recommendations in PSGs

> This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

- PSGs are published to facilitate generic drug development, not to discourage innovation.
- ANDA applicants can use alternative approach to recommendations in PSG if the alternative complies with applicable statutes and regulations.
- FDA recommends applicants contact FDA to discuss alternative approaches with FDA.

Pathways to Discuss Alternative Approaches with FDA

- Controlled Correspondence
  - Inquiries on a specific element of generic drug development (e.g., alternative proposal to PSG recommendations)
  - Not for general questions related to product planning
- Pre-ANDA Meetings (referenced in GDUFA II Commitment Letter)
  - Applies only to meeting requests for complex products
  - For example, utilized for discussion of specific scientific issues or questions related to proposed study design for complex drug products without PSGs

In Vivo BE Studies and Reference Standard

- For in vivo BE studies, an applicant must use the reference standard (RS) selected by FDA.
- See 21 CFR 314.3(b).
- Where the reference listed drug (RLD) *is marketed*, ordinarily it is also the drug product selected by FDA as the RS.

In Vivo BE Studies and Reference Standard, cont.

- Where the RLD has been *discontinued from marketing* for other than safety or effectiveness reasons, FDA may select a different listed drug as the RS.
- If the RS is not the RLD, the RS is not the basis of submission, but it should be identified in the relevant sections of the ANDA that include information pertaining to BE.

In Vivo BE Studies and Reference Standard, cont.

- If FDA selects an RS that is not the RLD for use in conducting in vivo BE studies, an applicant must demonstrate that its proposed generic drug meets the sameness requirements in section 505(j) of Food Drug & Cosmetic (FD&C) Act in relation to the RLD.
- Refer to guidance for industry, Referencing Approved Drug Products in ANDA Submissions (Oct. 2020) for more information on RS and RLD.

In Vivo BE Studies and Authorized Generics

- An ANDA applicant may use the authorized generic version of the RS in its in vivo BE studies.
- See section 505(t) of the FD&C Act for information on authorized generics.
- FDA recommends that applicants submit controlled correspondence to inquire further and to discuss necessary documentation before conducting studies.

https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/fda-list-authorized-generic-drugs

In Vivo BE Requirement Waivers

- In certain cases, the in vivo BE requirement can be waived (see 21 CFR 320.22).
- For example, for certain drug products, requirement can be waived for one or more strengths based on (1) acceptable BE study on the designated strength; (2) acceptable in vitro dissolution testing of all strengths; and (3) proportional similarity of the formulations across all strengths.

In Vitro BE Studies

- There are certain circumstances in which BE can be evaluated using in vitro approaches under 21 CFR 320.24(b).
- In such circumstances, the in vivo data requirement is not waived.
- Rather, FDA has determined that in vitro data are the most accurate, sensitive, and reproducible approach.

In Vitro BE Studies, cont.

- For in vitro testing, the regulations do not require that an applicant use a particular product as the reference product.
- FDA recommends that when applicants conduct in vitro BE testing, such testing be conducted with the drug product FDA selects as the RS.

Revised PSGs

- Bioequivalence Recommendations for Specific Products (June 2010) describes FDA's process for making PSGs available.
- PSGs are revised as appropriate to ensure most up-to-date BE information is available.
- Consistent with 21 CFR 320.24, BE recommendations in PSGs (new and revised) represent FDA's current thinking on the most accurate, sensitive, and reproducible approach for conducting BE testing.

Summary

- Regulations, such as 21 part 320, are requirements and are binding on the public and FDA.
- PSGs contain recommendations which reflect FDA's thinking on the most accurate, sensitive, and reproducible approach to BE testing, consistent with 21 CFR 320.24.
- Applicants can use an alternative approach if it complies with applicable statutes and regulations.

Resources

- Guidance for Industry, Bioequivalence Recommendations for Specific Products (June 2010)
- Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions (Oct. 2020)
- Guidance for Industry, Controlled Correspondence Related to Generic Drug Development (Dec. 2020)
- Guidance for Industry, Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (Nov. 2020)
- PSGs for Generic Drug Development: https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development
- Upcoming PSGs for Complex Generic Drug Product Development: https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development


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