Introduction: Statistical Approaches to Establishing Bioequivalence

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A Quote

- **“If I have seen further, it is by standing on the shoulders of giants.”** -Sir Isaac Newton
- Newton was explaining that his ideas didn't come from him alone
- The draft guidance comes as a result of years of experiences in practice and knowledge accumulation from many scientists

History

- **1992:** an FDA guidance on Statistical Procedure for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design

- **1997:** a preliminary draft guidance entitled “In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches” (62 FR 67880, December 30, 1997)

- **1999:** A draft guidance entitled “Average, Population, and Individual Approaches to Establishing Bioequivalence” (64 FR 48842, September 8, 1999)

- **2001:** The guidance for industry entitled “Statistical Approaches to Establishing Bioequivalence” (66 FR 8805, February 2, 2001)

- **2022:** The draft guidance for industry entitled “Statistical Approaches to Establishing Bioequivalence” (87 FR 74426, December 5, 2022)

The Guidance

- This statistical guidance is one of a set of core guidances being developed to provide recommendations on how to meet the provisions of part 320

- Requirements of bioavailability (BA) and bioequivalence (BE); and the types of in vitro and in vivo studies that are appropriate to measure BA and establish BE are set forth in part 320 (21 CFR part 320). This guidance provides recommendations on how to meet provisions of part 320 for all drug products

- Once finalized, it will represent the agency's current thinking on the statistical approaches used in BA and BE studies. It does not establish any rights for or on any person and is not binding on FDA or the public. An alternative approach may be used if such an approach satisfies the requirements of the applicable statutes, and regulations

A Combined Effort

- Office of Generic Drugs
  - Office of Research & Standards
  - Office of Bioequivalence
  - Office of Safety and Clinical Evaluation
  - Office of Generic Drug Policy
- Office of Translational Sciences
  - Office of Biostatistics
  - Office of Clinical Pharmacology
- Office of Pharmaceutical Quality

Content

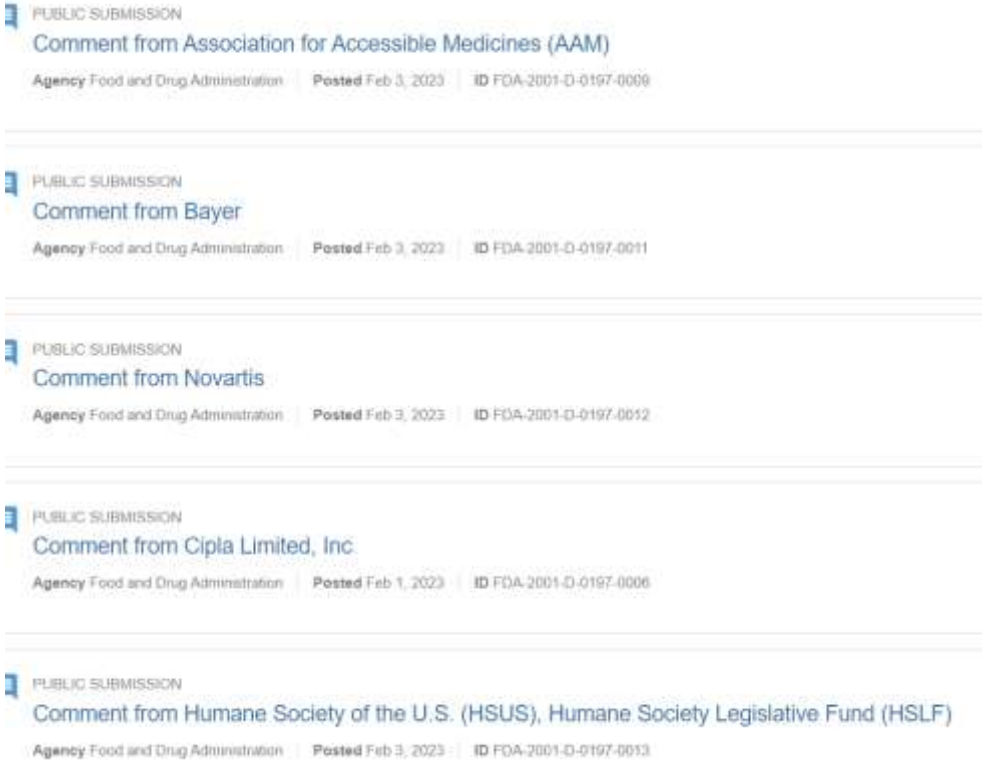
- Recommendations on the topics covered in the 2001 guidance as well as recommendations on additional topics, including missing data and intercurrent events, adaptive design, and specific situations, such as narrow therapeutic index drugs and highly variable drugs

- Recommendations to sponsors and applicants who intend to use equivalence criteria in analyzing in vitro or in vivo BE studies for INDs, NDAs, ANDAs, and supplements to these applications

- Statistical approaches for BE comparisons and focuses on how to use these approaches both generally and in specific situations

Comments Received

- https://www.regulations.gov/docket/FDA-2001-D-0197
- Deadline for Comments: February 3, 2023
- Number of Comments received: 101



Final Notes

- Some of the contents are being developed in accordance with relevant ICH guidelines and FDA guidances (e.g., ICH draft guideline - M13A Bioequivalence for Immediate Release Solid Oral Dosage Forms, January 2023)
- A clear path for certain topics are still under development, e.g., BE using multiple references
- When finalized, it will replace the 2001 guidance on the same topic