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February 2, 2023

IPAC-RS Comments on Draft FDA Guidance for Industry "Statistical Approaches to Establishing Bioequivalence"

(https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-approaches-establishing-bioequivalence-0)

The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) is an international association of companies focusing on orally inhaled and intranasal products. Member companies of IPAC-RS develop, manufacture and market both brand-name and generic products (see the list of members at https://www.ipacrs.org/about).

IPAC-RS seeks to advance the science, and especially the regulatory science, through joint research, consensus building, development of best practices, and collaborations among stakeholders.

The IPAC-RS Bioequivalence Knowledge Network reviewed the draft guidance "Statistical Approaches to Establishing Bioequivalence" with great interest, and would like to offer the following comments.

Please contact IPAC-RS Secretariat with any questions.

GENERAL COMMENTS

The confounding influence of between-batch PK variability on PK BE testing for locally-acting inhaled products has been a topic of dialog among industry and regulators for over a decade, yet no regulatory guidance exists to inform applicants of even general regulatory thinking on this topic. This issue may impact other low-bioavailability drugs, beyond the field of inhaled medicines. IPAC-RS therefore proposes the below specific text, which communicates the important and helpful message that the Agency will allow use of multiple RLD and/or Test batches in PK BE testing. Use of multiple batches can offer regulators and applicants lower BE decision error rates (both false positive and false negative).

Additionally, text is proposed to describe general guidance for applicants who may be considering use of reference-scaled average BE in the context of a multiple-batch study design, and/or expansion of reference-scaled statistical methods to accommodate within-subject variability from a between-batch source.

The specific in vitro BE criterion discussed in Section III subsections A1 to A6 somewhat correspond to either a specific dosage form and/or specific in vitro test where specific FDA guidances are cited.

In general, this guidance discusses the use of a single in vitro BE criterion for each specific situation; however, the cited guidances may allow or even stipulate the use of other BE criterion under certain circumstances.

COMMENTS ON f2 (lines 555-560)

Equivalence analysis of dissolution profiles is a multivariate equivalence testing problem. Guidelines on that topic and the original publication of f2 (from Moore and Flanner 1996) date from the mid-1990s, when the knowledge about multivariate equivalence tests was limited.

f2 (at first published in a non-statistical journal) is a series of monotone transformations of the Euclidean distance. These transformations provide no benefit, but they mask the fact that f2 is only a point estimate which does not allow Type I Error (TIE) control. Decision making without TIE control is not a scientific state of the art today. Please note that other considered methods in the guidance (ABE, PBE) provide at least approximate TIE control.

Today, it would be necessary to define the estimand for dissolution profile studies. Maybe the appropriate estimand depends on the product under investigation. Suggestions on the choice of estimands based on product characteristics are available (see "Dissolution profile similarity analyses – statistical principles, methods and considerations". *The AAPS Journal.* 2022; 24:54: https://link.springer.com/article/10.1208/s12248-022-00697-y). That paper presents valid equivalence tests with at least approximate TIE control for all discussed estimands/statistical hypotheses, even for the hypotheses behind f2.

The f2 similarity approach was recommended in 1995 SUPAC-IR Guidance without sufficient detail for implementation; by 1997 a complementary Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms was issued that actually limited the use of the f2 metric when certain conditions were not met. Even now after 25 years, questions and uncertainty still abound on how and when to use that specific in vitro BE criterion. Although this guidance is intended to encourage the use of science-based approaches to making statistical in vitro BE assessments, the in vitro BE area still suffers from the lack of a holistic approach as has been taken in the in vivo area.

SPECIFIC COMMENTS

Line	Comment and Rationale	Proposed change
736	Need to distinguish dispositional (between-occasion) from between-batch sources of within-subject PK variability.	Replace with "2. Statistical Method for Drugs with High Dispositional Variability"
738	Need to distinguish dispositional (between-occasion) from between-batch sources of within-subject PK variability.	Replace with "If a drug has high within-subject dispositional (i.e., between-occasion) variability, ..."
756	Add text pertaining to high within-subject between-batch variability.	Some drugs may display PK variability between manufacturing batches. As with high dispositional (between-occasion) variability, a characteristic of drugs that display between-batch variability is low bioavailability. For these drugs, applicants may consider inclusion of multiple batches of the RLD and/or Test product to increase the accuracy of the bioequivalence assessment (see Performance of Multiple-Batch Approaches to Pharmacokinetic Bioequivalence Testing for Orally Inhaled Drug Products with Batch-to-Batch Variability. AAPS PharmSciTech 2021). If multiple RLD and/or Test batches are used, applicants should compare the average PK parameter of all RLD batches to the average PK parameter of all Test batches used in the PK bioequivalence study. Statistical analysis using reference-scaled average bioequivalence should distinguish between-occasion and between-batch PK variability (i.e., applicants should not simply identify all of the data from the multiple RLD batches as "Reference" and then analyse the data as if the study had used a true replicate design). Applicants should consider the alignment between each source of variability and its corresponding degrees of freedom (related to the number of batches for between-batch variability, or the number of Test/Reference observations for between-occasion variability). Applicants considering use of between-batch variability in a reference-scaled statistical approach should address whether the number of batches is adequate to ensure accurate estimation of RLD between-batch variability, analogous to the requirement to include an adequate number (minimum of 24) of subjects to ensure accurate estimation of RLD between-occasion variability. Applicants are encouraged to contact the Agency early to discuss their proposed study designs and statistical methods.