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Demonstrating Bioequivalence for Locally Acting/Targeted Delivery Drugs

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Bioequivalence studies play a crucial role in drug development as companies pursue line extensions, make manufacturing changes, develop generic drugs and seek US Food and Drug Administration (FDA) approval via the abbreviated drug approval pathway known as 505(b)(2). This drug approval pathway relies upon "at least some of the information from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference," helping the sponsor win approval of a new strength, new dosage form or new route of administration for an existing drug without the time and cost of duplicating safety and efficacy studies previously conducted by the innovator company.[1] The sponsor of a 505(b)(2) application in these scenarios would need to demonstrate bioequivalence of the new dosage form, route of administration, etc. to the referenced product that was previously approved by FDA.

In 21 CFR 320.1, bioequivalence is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."[2] The FDA requirements for bioequivalence endpoints vary according to the route of administration and whether these products have systemic, or locally acting/targeted delivery implications.

Systemic drugs are delivered to the bloodstream for distribution to site(s) of action in various parts of the body. Plasma concentrations generally serve as a surrogate for the drug concentration at the site of action. On the other hand, locally acting/ targeted delivery drugs do not enter the bloodstream. They are delivered directly to sites of action, whether the mouth, eyes, ears, nose, lungs, gastrointestinal tract, skin, etc.[3] Examples of locally acting/targeted delivery drugs include:

- orally inhaled drugs
- nasal sprays
- dermatological products
- antifungal creams and suppositories
- oral medications for oral candidiasis
- eye drops for conjunctivitis
- ear drops for external otitis

The methods available to perform bioequivalence testing under various circumstances include: [4]

- pharmacokinetic (PK) studies
- pharmacodynamic (PD) studies
- comparative clinical trials
- *in vitro* tests such as dissolution testing, binding assays
- other methods deemed appropriate by FDA

Demonstrating bioequivalence using conventional methods such as PK bioequivalence studies alone can be meaningless for locally acting/targeted delivery drugs as often it is difficult to measure drug concentrations at the site of action. Also, the "drug may be able to reach the plasma without passing through the site of action;" for example, for inhalation products, some of the drug may be swallowed and hence orally absorbed.[5] This article presents techniques for demonstrating bioequivalence for several types of locally acting/targeted delivery drugs: orally inhaled drugs, nasal sprays and dermatological products.

Bioequivalence of Inhalation Products

FDA uses the "weight-of-evidence" approach in determining bioequivalence of orally inhaled products, which includes sameness of formulations in terms of qualitative and quantitative attributes, comparative systemic exposure, delivery of drug via *in vitro* performance of the delivery devices, and of course delivery the drug to local site of action. [6]

Various techniques to show bioequivalence of orally inhaled products include the following:

Use of Molecular Imaging

If imaging techniques can be used to develop and validate *in vitro* methods to quantify the amount of drug at the site of action, such information can be used to measure local delivery and hence provide *in vitro/in vivo* correlation.[7] For orally inhaled products such as Advair, this would include taking images of the lungs to determine particle deposition per quantified administration (such as one inhalation). Measurement of the particle deposition in essence will then serve as the measure of local delivery for that drug and would provide data for *in vitro/in vivo* correlation.[8] One non-invasive imaging technique known as gamma scintigraphy has been shown to measure

local bioavailability of drug deposition in the lungs.[9] Other techniques include photon emission computed tomography and positron emission tomography.[10]

Modified Pharmacodynamic Study Designs
Use of routine pharmcodynamic study designs to show bioequivalence of asthma drugs would require very large number of patients due to many factors such as known shallow dose-response curve, high variability within and between subjects.[11] This is cost prohibitive for many generic companies looking to make copies of innovator asthma drugs. If the pharmacodynamic study design is modified to include FEV1 endpoint (forced expiratory volume in 1 second) in a crossover study design, number of subjects required in a study would be low.[12]

Combining Endpoints for Multiple Active Ingredients
When a product contains more than one active ingredient, local delivery of all active components must be equivalent to the innovator product to demonstrate bioequivalence. For example, if the combination drug product comprises an inhaled corticosteroid and a long-acting beta-agonist, bioequivalence at local delivery for both components must be demonstrated.[13] It needs to be noted that "the FEV1 endpoint is initially affected by the beta-agonist and affected by both components at later times. An exhaled nitric oxide (eNO) endpoint is affected only by the inhaled corticosteroid. Combining these endpoints could potentially allow bioequivalence determinations for both components."[14]

Measurement of Reversibility in COPD Study Designs
It is well known that various bronchodilators provide varying degrees of reversibility for chronic obstructive pulmonary disease (COPD) such as chronic asthma, emphysema, chronic bronchitis, etc.). In order to assess dose-response relationship for the various diseases that fall into this category, measurement of reversibility for each subgroup of COPD is needed. Dose selection and understanding of systemic exposure of poorly absorbed drugs are also necessary when designing the bioequivalence study.[15]

Assessment of Formulation Differences
For bioequivalent drug products, FDA expects bioequivalent inhalation products to be qualitatively and quantitatively similar to the reference listed drug (RLD). The active ingredient(s) have to be exactly the same as the RLD, and the inactive ingredients, generally have to be within ±5% of those used in the RLD.[16, 17] Other factors in the formulation of the drug product that play a critical role are the "size, shape, surface properties, and morphology of drug and carrier particles," as they can impact drug deposition in the lungs.[18] Any and all differences and their impact on the drug's safety and efficacy need to be explored. For example, if different amounts of excipients are used, it will need to be shown that this does not impact aerosol particle behavior of the drug or target delivery dose. What types of studies would need to be conducted will depend upon the differences in formulation.

For dry powder inhalation products, thorough studies should be undertaken to understand not only any drug formulation differences, but also how the device performs for the test product compared with the RLD. The following *in vitro* tests can be conducted on the device performance to show equivalence: measurements of droplet size distribution, plume geometry, and spray pattern. Quality specifications can be established to show equivalence based upon the collected data.

Bioequivalence of Nasal Sprays

FDA may grant biowaiver(s) for nasal solution sprays that contain the same active and inactive ingredients in the same concentrations as RLD, if comparability can be shown in *in vitro* tests such as drug release test, impurity profile, etc. To show equivalence of nasal suspension sprays on the other hand, is more involved and should include *in vitro* tests examining "droplet size distribution, plume geometry, and spray pattern."[19] If these parameters are equivalent for the RLD and the test product, FDA may waive *in vivo* studies. Pharmacokinetic studies should be performed to assess any differences in systemic exposure.

Bioequivalence of Topical Dermatological Products

The bioequivalence approach for topical dermatological products varies depending upon the product. As shown in the following sections below, different types of information are required to show bioequivalence for solutions, creams and lotions.

Bioequivalence of Topical Solutions May be Self-Evident
The bioequivalence strategy for topical solution prescription drug products is very similar to that previously provided for nasal solution sprays. The topical solution product that contains the same active and inactive ingredients in the same concentrations as RLD should be eligible for biowaiver for clinical studies, if comparability can be shown in *in vitro* tests such as drug release test, impurity profile, etc.[20]

Bioequivalence of Topical Creams Using DPK Testing
In addition to demonstrating use of the same active ingredient in the same concentration, the company should show that the vehicle in which the active component is dissolved is the same as the RLD.[21] Since systemic exposure to topical drugs is next to impossible to measure due to low levels in bodily fluids, FDA recommends using a pharmacokinetic approach called dermatopharmacokinetic (DPK) testing, in which the product is applied to the stratum corneum based on a "stratum corneum concentration-time curve," meaning that drug concentration is measured with respect

to time and the data collected provides information on drug uptake, steady-state levels, and drug elimination from the stratum corneum.[22] DPK principles can be applied to show bioequivalence of topical drug products such as antifungal, antiviral, anti-acne, antibiotic, corticosteroid and vaginal creams. DPK studies should be conducted in healthy subjects. Validation of both analytical methods and the technique of skin stripping is needed for DPK studies.

Other ways to measure local delivery of topical dermatological products include:[23]

- Microdialysis, which involves insertion of a semipermeable capillary tube into the dermis (approximately 1000 mm under the skin.) It is expected that drug will enter the capillary tube from the surrounding extracellular fluid of the tissue where the topical drug was applied.
- Near-infrared spectroscopy is able to detect unique signals for varying concentrations of drug.

Bioequivalence of Topical Corticosteroid Creams/Lotions via Pharmacodynamic Studies and Various other Studies

The number of studies required to show bioequivalence for topical corticosteroid lotions and creams may vary. For example, FDA recommends conducting vasoconstrictor studies that include a pilot dose duration-response study followed by the pivotal *in vivo* bioequivalence study in healthy subjects. Topically applied corticosteroids are known to produce a vasoconstrictor effect that results in skin blanching. This pharmacodynamic (PD) response has been correlated with corticosteroid potency and efficacy.[24] In addition, FDA may also require a randomized, double-blind, parallel, placebo-controlled, *in vivo*, clinical endpoint bioequivalence study in subjects with the particular dermatological condition.[25]

It is highly recommended that the sponsor consult FDA's Bioequivalence Database to garner insights into study design and duration, and the availability of appropriate scales to be used from similar products. This database provides draft guidance and/or final guidance for specific drug products that are already approved:[26]

- Number of recommended studies
- Type of study that should be conducted
  - PK study: whether under fed or fasting conditions; information on study design; whether bioequivalence should be based on a 90% CI
  - Clinical endpoint bioequivalence study: details regarding clinical endpoints; diagnostics tests; inclusion and exclusion criteria; whether placebo arm is recommended; rescue medicines, etc.
- Analytes to measure (definition of appropriate biological fluid)
- *In vitro* testing, if applicable

Clinical endpoint studies are generally expensive to conduct as they may require several hundred patients and last for several weeks.[27] To ensure that the study is sensitive enough to show any difference between the test product and the RLD, both the test product and the RLD must be statistically superior to placebo ($p<0.05$).

Conclusion

Unique challenges confront companies attempting to show bioequivalence of locally acting and targeted delivery drugs. A prudent first step is to conduct thorough research of the literature and the FDA Bioequivalence Database, which is a great resource for information on which types of studies have been required by the agency for similar products. One way to reduce the amount of work involved in proving bioequivalence to existing drug products is to plan a drug development strategy that involves quantitative and qualitative equivalence to active and inactive components of drug formulation.

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