Strategies for the Equivalence Assessment of Locally Acting Complex Drug Products:
Focus on Alternative Methodologies

The Regulatory Sciences section submitted this article.
Complex drug products (CDPs) comprise a growing pharmaceutical sector, due to the safety, efficacy, and compliance benefits they provide. CDPs include those with complex active ingredients (e.g., peptides, natural source products), complex formulations (e.g., liposomes, iron colloids), complex routes of delivery (e.g., locally acting drugs), and drug-device combinations (e.g., inhalers, nasal sprays, auto injectors, and transdermal systems). As reflected in recent regulatory science initiatives by the Food and Drug Administration (FDA), there is a rising interest in making generic versions available for all CDP categories by applying a rational, science-driven approach that conceptually relies on quality by design. The current article discusses an integrated and dynamic methodology, centered on nonclinical techniques, for optimizing formulations and accelerating equivalence assurance of locally acting drug products, a subset of CDPs.

CHALLENGES IN ESTABLISHING EQUIVALENCE FOR LOCALLY ACTING DRUG PRODUCTS

According to FDA, generic drug products must meet the same standards of quality, efficacy, and safety as their reference listed drug (RLD) counterparts. Therefore, procedures are established to demonstrate that generic products are therapeutically equivalent and interchangeable with such. Therapeutic equivalence (TE) is generally achieved by assuring pharmaceutical equivalence (PE) and bioequivalence (BE) of the generic to the RLD products.

Drug products are pharmaceutically equivalent when they contain the same active ingredient(s), are of the same dosage form and route of administration, and are identical in strength or concentration. Drug products are bioequivalent when the rate and extent of absorption at the site of drug action are not significantly different when administered to patients or subjects at the same molar dose under similar conditions. FDA regulation 21 CFR §320.24(b) provides a list of methods for establishing BE in descending order of accuracy, sensitivity, and reproducibility as follows: in vivo concentration of active moiety in human biological fluid, in vitro test that has been correlated with and is predictive of human bioavailability data, in vivo evaluation based on urinary excretion, in vivo measurement of an acute pharmacological effect, well-controlled clinical trials that establish the safety and effectiveness of the drug product, a currently available in vitro test (e.g., dissolution rate test) acceptable to FDA, and any other approach FDA deems adequate.

For solid oral drug products intended for systemic delivery, human pharmacokinetic (PK) studies supported by in vitro dissolution are largely successful in establishing BE. For locally acting drug products, such as topical dermal and ophthalmic formulations, establishing equivalence often proves to be more challenging. In such cases, plasma concentrations may not be an accurate measure of drug availability as these are downstream to the site of action. Direct measurement of the active ingredient locally can also be unreliable due to variations in application area and/or duration of exposure. Physiology of the skin and eye, including numerous pathways for drug absorption and changes in the diseased state, also contribute to overall variability.

Consequently, and with few exceptions, BE methods for such products are restricted to clinical endpoint studies because all drugs have a clinical endpoint that was used to support their initial approval. This approach, which FDA states to be the “least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating equivalence” (21 CFR §320.244), typically consists of a three-arm comparative efficacy trial in which the RLD
and generic are each tested vs. placebo in a relevant patient population for the approved indication. In addition to meeting the equivalence requirements between generic and RLD, both the generic and RLD formulations must demonstrate statistically significant improvement over the placebo group. Exceptions to clinical endpoint equivalence studies are available for certain products based on their mechanism of action, drug substance properties, or nature of the reference formulation. Examples of such products include: corticosteroids for which skin blanching (a pharmacodynamic endpoint) may be utilized as an indirect measure of local drug concentrations, local anesthetics (e.g., lidocaine) with measurable systemic drug concentrations for which well-controlled PK studies are used, and topical solutions (e.g., fluorouracil) for which equivalence is implicit when formulations have the same qualitative (Q1) and quantitative (Q2) composition as the RLD product.

The high variability and low sensitivity of clinical endpoint trials introduce substantial technical difficulties and necessitate large studies at high cost. These hurdles have produced a major barrier to the development and registration of dermal and ophthalmic locally acting generic products. The burden also affects the drug innovators, who must demonstrate equivalence between batches for scale-up and postapproval changes. There is a clear need to expand the use of alternative methodologies for equivalence assessment outside these few product- or mechanism-specific examples.

CHARACTERIZATION-BASED EQUIVALENCE AS AN ALTERNATIVE

Recognizing the need for more efficient BE methods and the general “market failure for innovation,”5 FDA has issued a few draft guidance documents with simplified BE requirements for locally acting drug products in recent years. Such guidances, including those for cyclosporine ophthalmic emulsion7 and acyclovir ointment,6 are published on a case-by-case basis within product-specific BE recommendations. Most notably, they permit the use of in vitro methods that utilize the principles of biopharmaceutics in lieu of clinical endpoint studies for establishing equivalence of generic formulations with identical compositions of inactive ingredients. These “in vitro only” exceptions seem to apply when a confluence of factors is present, including: product need (i.e., no patents or exclusivity on the RLD product but patient access remains limited and expensive due to the lack of generics); difficulty with meeting agency-recommended BE requirements (e.g., difficulty demonstrating superiority over placebo, even for the RLD product); and most important, availability of in vitro methods that provide a more accurate, sensitive, and/or reproducible assessment of BE than the only viable alternative (i.e., clinical endpoint studies). Arguably, however, these scientific principles of biopharmaceutics could similarly be applied for equivalence of CDP outside these product-specific examples.

Biopharmaceutics is the study of the physical and chemical properties of drugs and the biological effects they produce.9 Understanding these factors and identifying the rate-limiting steps that influence rate and extent of absorption allow for the inference of equivalence without performing and/or repeating clinical studies. For over a decade, FDA has permitted waivers of clinical PK BE studies for drugs that possess intrinsically high solubility and permeability (based on in vitro measurements) in rapidly dissolving immediate-release solid oral dosage forms. According to the principles of the Biopharmaceutics Classification System (BCS), such drugs should always exhibit complete oral absorption (>90 percent), and their BE is self-evident, as long as the inactive ingredients do not significantly affect absorption of the active ingredients.10 BCS is one of the best examples of a successful regulatory science initiative, resulting in biowaivers for dozens of oral products and improving patient access to low cost generic medicines, while reducing the extent of human testing.

Along these lines, for certain locally acting semisolid formulation types (e.g., simple suspensions and low viscosity emulsions), comparative release rates of drug from the formulation reflect the combined effect of drug and formulation and may serve as a surrogate for equivalence in rate and extent of drug absorption. These release rates are controlled by physical and chemical properties of the drug product, which in turn are impacted by the variables within...
Drug release characteristics from the finished product have the potential to alter the biological performance of the drug in the dosage form. Therefore, product performance tests are conducted to assess drug release from the finished dosage form. Release of drug from the formulation is typically measured across a synthetic membrane using a vertical diffusion cell system (Franz cell diffusion system or, in some cases, a modified holding or extraction cell). A layer of the test semisolid is placed in contact with a reservoir, and diffusion occurs between the delivery system and reservoir through an inert support membrane. Samples are withdrawn from the reservoir at various times and the in vitro release rate is calculated.

This method, which is outlined in FDA’s Semisolid SUPAC Guidance, has traditionally been used to evaluate scale-up and postapproval changes of the same manufacturer and is now extended for equivalence testing of generic drug products. This shift from the traditional paradigm of “equivalence by clinical endpoint comparison” towards “characterization-based equivalence” (CBE) for locally acting drug products signifies the trend toward a rational, science-driven approach (Figure 1). The current framework encourages the use of appropriate surrogates to target “pharmaceutical equivalence by design.” The recent “in vitro only” equivalence recommendations for locally acting semisolids highlight an evolution of biopharmaceutics, which will accelerate generic drug development for CDP. The progression toward CBE has resulted in a more efficient product approval process with greater emphasis on PE and fewer TE risks managed by in vivo BE. In addition to supporting regulatory equivalence endpoints, biopharmaceutics principles may also be employed to guide formulation development, predict in vivo performance, establish critical manufacturing variables, implement quality control, and evaluate postapproval changes.

BUILDING WEIGHT OF EVIDENCE

Even as CBE marks progress from clinical endpoint studies to in vitro approaches for specific products and the possibility of extending this concept to all well-defined formulation types, there remain many complex drug products and formulations (e.g.,

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**Figure 2. Building Weight of Evidence for Equivalence Evaluation of Complex Drug Products**

1. Equivalence assessment with a single set of tools
2. Equivalence agreement between orthogonal measurements
3. Agreement in combined approaches to enhance equivalence assurance
mixtures with molecular diversity, multiphasic formulations, etc.) where demonstration of BE remains a challenge as properties that govern rate and extent of drug absorption at the site of action are not clearly understood.

In such cases, TE may be established by augmenting CBE with additional product performance testing to build a “weight of evidence” approach to equivalence (Figure 2). Various nonclinical methods, including in vitro, ex vivo, and nonclinical in vivo techniques, may support CBE and build confidence in CDP performance. For such formulations, additional endpoints that mimic physiological response or biological behavior may be appropriate to reduce or eliminate any residual uncertainty with demonstrating equivalence. These could include accumulation of drug in target tissues for better correlation to its effect or other means of bio-characterization using systems and methodologies that are sensitive to formulation changes. Examples include human or animal tissue (i.e., when the bio-membrane is conserved across species) mounted in Franz diffusion chambers or Ussing chambers. Drug penetration across such tissues (including cornea/conjunctiva, skin, intestine, inner cheek, vagina, etc.) may be evaluated to determine feasibility of alternative drug delivery routes, compare formulations during development, assess both release and target tissue-specific drug accumulation, investigate biochemical interactions, and/or evaluate regional absorption. Additionally, distribution in the adnexa for investigation of safety may be quantified in PK studies, and translatable nonclinical diseases models can be used to develop confidence in a product before a clinical investigation. Demonstrating equivalence with orthogonal measurements and using this combined methodology for building “totality of evidence” at one specified dose strength may also allow the possibility of more limited comparative testing across the remaining product strengths.

BIOPHARMACEUTICS FOR THE FUTURE

Recent regulatory guidances, as well as FDA’s ongoing research priorities under the newly enacted Generic Drug User Fee Act, underscore the increasing importance of characterization-based equivalence for evaluating performance and therapeutic equivalence of CDP. Applying a rational, science-driven approach by integrating various nonclinical techniques extends the impact of biopharmaceutics and accelerates development of therapeutically equivalent CDPs, while providing BE assessments that are more accurate, sensitive, and reproducible than traditional clinical endpoint studies.

REFERENCES


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DISCUSSION POINT

We want to know your opinion!
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What can be done to facilitate adaptation of alternative methodologies for equivalence evaluation of complex drug products?