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Novel Approaches of Demonstrating Bioequivalence

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Introduction

The Drug Price Competition and Patent Term Restoration Act (Public Law 98-417) of 1984 have made drugs more accessible. One of the key elements of the Act is the demonstration of bioequivalence of generic products containing drugs that are not eligible for bioequivalence waiver. Bioequivalence testing originated in the early 1970s with the ±20 rule. According to a separate study, "the shortcomings of this approach were immediately evident, since such a criterion would theoretically allow the parameters of generic product A to differ from the reference (innovator) product by +20%, while allowing the parameters of generic product B to differ from the reference product by -20%. The net difference between the generic products A and B would then be as much as 40% and, therefore, beyond the limits of therapeutic equivalence as originally conceived[1]." In response, the FDA adopted a powered approach in the early 1980s. However, both approaches were discontinued by the FDA in 1986 because of public concern about bioequivalence and were subsequently replaced by the 90% CI approach in 1992, which remains the current criteria for bioequivalence decisions[2].

How closely the FDA sticks to this guidance is seen in the current bioequivalence testing guidance that states[3] that "We recommend that applicants not round off CI values; therefore, to pass a CI limit of 80 to 125 percent, the value should be at least 80.00 percent and not more than 125.00 percent."[The upper limit of 125.00 percent comes from the strict 20.00% limit on each end (100/125=0.80)]. Why is there a need to follow this limit so strictly? According to the FDA[4], this range is based on a clinical judgment that a test product with bioavailability that falls outside this range should be denied market access. A 90% CI is used, since a 5% statistical error is allowed at both the upper and the lower limits. Therefore, the total error is 10%, generating the 90% CI. Understanding a predefined range is much more intuitive and easier to grasp than the reality of multiple PK parameters having to fit within a narrow CI.

Now that the FDA has initiated its efforts to bring innovation to the Act, I would like to suggest that we re-examine the current the guidance on how to meet the BA and BE requirements set forth in 21 CFR part 320 as they apply to dosage forms intended for oral administration or non-orally administered drug products when reliance on systemic exposure measures is suitable to document BA and BE (e.g., transdermal delivery systems and certain rectal and nasal drug products). A suggestion for this change comes in The Patient Protection and Affordable Care Act (Affordable Care Act), signed into law by President Obama on March 23, 2010, that amends the Public Health Service Act[5] (PHS Act) to create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with a FDA-licensed biological product. This pathway is provided in the part of the law known as the Biologics Price Competition and Innovation Act (BPCI Act). Under the BPCI Act, a bio-similar product is a biological product that is approved based on a showing that it is highly similar toa FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product.

What I am proposing is that we add the consideration of "clinically meaningful" to the bioequivalence testing of generic products, instead of using a fixed range of bioequivalence, to make this test more relevant. An FDA analysis shows that for the submissions between 1996 to 2001 for highly variable drugs, the mean AUC varied by[6] 10%, while the range allowed was 20%. Such statements can be misleading since they do not represent the granularity of data where even 10% variability can be too much and the situations where 30% variability will still yield a clinically equivalent product. The FDA has recently begun discussion of narrow therapeutic index (NTI) drug bio-equivalence[7]. Four new draft guidances are posted online recommending replicate design

[1]Henderson JD, Esham RH (2001) Generic substitution: issues for problematic drugs. South Med J 94(1): 16-21.
[2]https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf
[3]https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf
[4]Buehler G. History of bioequivalence for critical dose drugs. FDA.
[5]https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/
[6]https://www.google.com/search?q=how+did+fda+decide+on+80-125%25+limit&oq=how+did+fda+decide+on+80-125%25+limit&aqs=chrome..69i57.10095j0j4&sourceid=chrome&ie=UTF-8
[7]https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm500577.htm

studies for NTI drugs including tacrolimus, phenytoin tablet, levothyroxine, and carbamazepine. The movement from "one size fits all" to product-specific standards is a sign of the maturation of the generic drug program. However, the emphasis in these recent approaches has been on the statistical design and not the margin that remains an iron-clad acceptance criterion. Replicate design helps reduce the size of the study, yet it does not add a clinically meaningful component to the study.

I am recommending that the FDA allow developers to justify margin that they can demonstrate to provide a clinically meaningful comparison that may include novel in vitro testing methods or any other approaches that have not been explored mainly because of the fixation of complying with the equivalence margins as currently mandated. The roots of this recommendation come from the 21 CFR Part 320[8] where in: "(e) Bioequivalence means 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." Since the site of drug action as cited here is in most case not known and rarely sampled, blood level PK studies were suggested as a surrogate, not a primary test, to demonstrate bioequivalence. In fact, given that blood level studies add substantially more variability in the assessment of bioequivalence, better means of establishing bioequivalence are the in vitro means wherein a generic product is more likely to show a discernible difference. One such means is demonstration of thermodynamic equivalence for which a Citizens Petition is already filed and opens for comments.

Thermodynamic equivalence (TE) is by another name, the "basis" for bio-waivers, in place for years. For a highly soluble drug, the barrier Delta G is small, overcoming any differences between two products. I am expanding this concept to drugs subject to blood level studies. Why would a drug product fail in BE, when it has the same chemical entity? It is inevitably the release profile at the site of delivery, since this point forward, all factors apply equally. Dissolution rate testing is the best example of measuring chemical potential and while it works well for products with small DG, it fails for drugs that are not released instantly. Creating a matrix of dissolution profiles, independent of any physiologic conditions, may be able to discern the differences not picked up by current dissolution testing. The TE provides a better estimate of the equivalence of the generic and the reference product at the site of administration, a more important attribute since the rest of the complexity and variability stays common with both the generic and reference product. The test of TE can be extended to provide a continuous monitor of bioequivalence of the generic drug over the lifecycle of the reference product, an attribute that is currently not required for testing.

The Public Law 98-417 has served the US citizens well; now it is time that we examine its components utilizing the novel approaches to improving upon its utility, and it requires abandoning the arbitrary equivalence criteria and a redundant blood level study that was a surrogate in the first place, and need not be retained unless proven to bring a greater understanding of any clinically meaningful difference between a generic and a reference product.

[8]https://www.gpo.gov/fdsys/pkg/CFR-2009-title21-vol5/pdf/CFR-2009-title21-vol5-part320.pdf