Risk Based Approach for Biowaiver Application to Immediate Release (IR) Solid Oral Dosage Forms
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Purpose
The in vivo studies measuring the bioavailability (BA) and/or bioequivalence (BE) during drug development play a pivotal role for bridging major formulation/manufacturing changes and/or demonstration of product strength equivalence. For orally administered drugs, the in vivo BA/BE study requirement, in certain instances, can be waived if the provisions outlined in regulations (21 CFR 320.22(d)(2) are met. The intricacy of the proposed change in certain situations may not fulfill the biowaiver criteria (e.g., compositional non-proportionality). This usually indicates the need of in vivo BA/BE studies. However, such scenarios call for considerations of relevant in vitro/in vivo data collected during drug development and risk-benefit assessment to judge on the clinical impact of not meeting the required criteria. Therefore, efforts were initiated with the objective to highlight the potential utility of a risk based approach which takes into consideration the clinical impact for regulatory decisions on biowaivers.

Methods
The biopharmaceutics component of New Drug Applications (NDAs) for approved solid oral dosage forms (2013-2014) were reviewed to identify complex biowaiver situations mentioned above and to study the associated biowaiver approach(es) used in regulatory decision making. From preliminary analysis, two immediate release (IR) drug products were identified as representative examples for a risk based biowaiver approach.

Results
Example 1 represented a case of dissolution dissimilarity in multiple media (f2 < 50; i.e., strength dependent dissolution) between the to-be-marketed (TBM) formulation of lower strength and clinical trial formulation (CTF, pivotal BE study) of higher strength of compositionally proportional IR oral tablets (Dissolution rate_{CTF/higher strength} < Dissolution rate_{TBM/lower strength}). The dissolution similarity testing conducted to support a minor change in product quality attribute for the higher strength also failed to meet similarity criteria (Dissolution rate_{CTF/higher strength} < Dissolution rate_{TBM/higher strength}). However, the biowaiver request for TBM product of both lower and higher strengths was adequately justified based on clinical risk-benefit assessment that considered the following: (1) comparable pharmacokinetics (PK) between IR tablets and capsules that failed dissolution similarity; (2) comparable PK of marketed solid oral dosage forms of this drug; (3) evidence of high solubility of drug substance across gastrointestinal pH range; (4) compositional proportionality; and (5) wide therapeutic index of the drug product. The risk assessment performed based on the available clinical and PK information supported that the risk of bio-inequivalence was low and the change in quality attribute would not impact the clinical performance and thus both strengths and pre- and post-change product were considered clinically equivalent.

Example 2 illustrates the use of comparative in vitro dissolution testing also through a risk based approach assessment to support major pre-approval formulation changes for an IR tablet. The change involved removal of an excipient and increase in the amount of diluent. The use of comparative in vitro dissolution testing for the demonstration of BE for a major change was justified based on (1) multimedia in vitro dissolution similarity between the formulations before and after the change; (2) use of prior knowledge on the safety profile of the drug for a similar formulation and systemic exposure indicating absence of safety concern due to anticipated slight increase in C_{max} as a result of expected faster disintegration; and (3) formulation changes were not expected to affect AUC since extent of dissolution was the same. Based on the knowledge of manufacturing process and material properties and the above information, the risk to clinical performance due to the formulation changes was considered low.

Conclusion
The above examples highlighted the potential utility of a risk based approach for regulatory decision making on biowaivers that considered the clinical impact that a formulation/manufacturing change could have based on comprehensive analysis of the available in vitro and in vivo information. These examples underscore the need for consideration of drug product behavior in vivo (safety profile, dose/response relationship, biopharmaceutics characteristics, etc.) for biowaivers based on a risk-based approach. The key to successful implementation of this approach is the analysis of clinical risks versus benefits for the drug product under question that would help making patient centric decisions.

*The findings and conclusions have not been formally disseminated by the FDA and should not be construed to represent any Agency determination or policy.