WORKSHOP: Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls

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Background

The role of biopharmaceutics in drug development is to ensure that drug release and absorption from the drug product results in optimal therapeutic efficacy and safety for the patient. As such, understanding the drug release mechanism and *in vivo* factors affecting the rate and extent of drug release are critical.

The assumption generally works *that two presentations of the same active drug moiety which deliver similar drug concentrations at the site of action (either systemic or local) can be considered as similarly efficacious. Therefore, the local and systemic exposure of drugs is a primary aspect of biopharmaceutics. In this regard, s*everal FDA guidance documents[i,ii,iii] advocate the use of biopharmaceutics tools such as *in vitro* dissolution, bioavailability (BA)/Bioequivalence (BE) assessment along with modeling and simulation approaches as the means to support drug product quality (e.g., following formulation and manufacturing changes) and as an aid to support regulatory decisions.

The advancements in science as well as modeling and simulation tools during the last decade now enable the development and application of physiologically based models which link physiological and physicochemical factors to assist drug development and regulation. In this regard, physiologically based pharmacokinetic (PBPK) modeling approaches have become a key tool to predict systemic exposure of the drug product[iv]. However, the typical inputs for current PBPK models only account for rudimentary properties of the formulation. Detailed assessment of compositional variations, manufacturing changes and the resulting formulation performance are not adequately translated into the current PBPK models, and thus it is challenging to predict the effect of such changes on local and systemic exposures in human. Thus, there is a need for the refinement of existing approaches (e.g. PBPK modeling) with a focus on translating the effect of formulation and manufacturing changes (e.g. biopharmaceutics analysis) into *in vivo* performance.

Ideally, to assess drug product clinical performance following formulation and manufacturing changes, biopharmaceutics models that capture the interactions between the physiology (i.e., by using physiologically based models) and the pharmaceutical formulation by mechanistic implementation of formulation/manufacturing aspects that are relevant to dissolution/release from the drug product are critical. Such models, namely physiologically based biopharmaceutics models (PBBM) should take into consideration factors beyond physiological and pharmacokinetic (i.e. ADME) components. They should define mechanistic elements of drug dissolution/release relevant to interactions of the pharmaceutical product with physiological conditions and events which can be parameterized to describe the key formulation characteristics. Once these mechanistic elements are defined, PBBM modeling can be used to predict the impact of variations in the critical material attributes (CMAs) and critical process parameters (CPPs through the establishment of a safe space via either IVIVCs or *in vivo-in vitro* relationships (IVIVRs) combined with virtual BE simulations. This approach will facilitate the incorporation of clinical relevance in product quality from initial development through marketing approval to lifecycle management and thereby minimize the need to conduct additional *in vivo* BE studies, leading to reducing cost in product development and supporting regulatory decisions.

[i] Dissolution guidance 1997
[ii] IVIVC guidance 1997
[iii] SUPAC guidance
[iv] Kostewicz, E.S., et al., PBPK models for the prediction of in vivo performance of oral dosage forms. Eur. J. Pharm. Sci., 2014. **57**: p. 300-321.