The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2020
Pharmaceutical Quality/CMC

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TABLE OF CONTENTS

The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides general recommendations regarding the development, evaluation, and use of physiologically based pharmacokinetic (PBPK) analyses for biopharmaceutics applications employed by sponsors of investigational new drug applications, and applicants for new drug applications, or abbreviated new drug applications, and supplements to these applications,[2,3] for oral drug product development, manufacturing changes, and controls. PBPK analyses use models and simulations that combine physiology, population, and drug substance and product characteristics to mechanistically describe the pharmacokinetic (PK) and/or pharmacodynamic behaviors of a drug product.[4]

The application of PBPK modeling in support of drug product development is an evolving field. We note that there are multiple terms used to describe PBPK analyses for biopharmaceutics applications, including PBPK absorption modeling (Zhang et al. 2017), physiologically based absorption modeling (Kesisoglou et al. 2016), and physiologically based biopharmaceutics modeling (PBBM) (Heimbach et al. 2019). This guidance uses the term *PBPK analyses (or*

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, *sponsor* refers to sponsors of investigational new drug applications, applicants for new drug applications and abbreviated new drug applications, and supplements to those applications.

[3] The scientific principles described in this guidance are applicable regardless of whether an original clinical study demonstrated bioavailability/bioequivalence and are relevant whether or not an application is required.

[4] Submission of PBPK analyses to FDA is discussed in the guidance for industry *Physiologically Based Pharmacokinetic Analyses — Format and Content* (August 2018). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

modeling) for biopharmaceutics applications to emphasize the focus on drug product quality attributes and a mechanistic understanding of their interaction with physiology to affect in vivo drug performance.

This guidance applies only to orally administered, systemically active drug products. It does not apply to locally acting drug products, including orally delivered gastrointestinal (GI) drug products that reach the site of action before entering systemic circulation. The use of PBPK analyses for biopharmaceutics applications for locally acting drug products will be considered on a case-by-case basis and via communication with FDA.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Several guidances for industry advocate the use of biopharmaceutics tools,[5] such as in vitro dissolution, and in vivo bioavailability (BA)/bioequivalence (BE) studies, along with modeling approaches to support drug product quality. In addition, quality by design (QbD) principles recognize that drug product quality cannot be tested into drug products; quality should be built into drug products by design.[6] In this regard, QbD enables an in-depth understanding of the relationship among critical quality attributes (CQAs), critical material attributes (CMAs), critical process parameters (CPPs), and predefined clinical performance metrics (e.g., systemic exposure such as C_{max} and area under the curve (AUC)). Data describing this relationship are essential for establishing an in vitro-in vivo link. Establishing an in vitro-in vivo link supports clinically relevant drug product specifications.

[5] See the guidances for industry *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997), *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* (September 1997), and *Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995).

[6] See the ICH guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

Although the pharmaceutical industry has in some cases been successful in developing in vitro/in vivo correlations (IVIVCs) to support biowaiver[7] requests in lieu of in vivo BE studies for major manufacturing changes (Nguyen et al. 2017), development of an adequate IVIVC for regulatory submission remains challenging (Suarez-Sharp et al. 2016). FDA recognizes this challenge and encourages the development and use of new tools and approaches for linking pharmaceutical quality to clinical performance. Advances in modeling and simulation have enabled the integration of factors such as the physicochemical properties of the active pharmaceutical ingredient (API), dissolution data, and the physiology of the GI tract into the development of PBPK models. As such, PBPK modeling has become a promising tool in predicting systemic drug exposure (Kostewicz et al. 2014a) and has been used for dose selection, food effect assessment, and drug interaction potential evaluation (Wagner et al. 2015a; Wagner et al. 2016; Huang et al. 2013; Wagner et al. 2015b).

III. IMPLEMENTATION OF PBPK MODELING FOR BIOPHARMACEUTICS APPLICATIONS

The application of PBPK modeling could be expanded to pharmaceutical drug product development, manufacturing changes, and controls. One feasible approach is to combine an in vitro drug product test (e.g., biopredictive dissolution) with PBPK models where in vitro dissolution data provide input to predict absorption (Heimbach et al. 2019). As such, dissolution testing is a key modeling input, because it probes both the extent and rate of in vivo drug product release.

The purpose of PBPK analyses for biopharmaceutics applications is to combine dissolution modeling/biopredictive dissolution or other in vitro testing inputs with PBPK modeling strategies to quantitatively describe (or characterize) the potential interactions of formulation variants with the body and their effect on drug exposure. This modeling approach should include relevant mechanisms pertaining to the absorption process, such as GI tract local metabolism (if applicable) and drug transport, and incorporate drug product quality properties to predict systemic drug exposure.

[7] In addition to waiver of an in vivo BE requirement under 21 CFR 320.22, there are certain circumstances in which BE can be evaluated using in vitro approaches under 21 CFR 320.24(b)(6). The scientific principles described in this guidance regarding waiver of an in vivo requirement also apply to consideration of in vitro data under that regulation. In such circumstances, an in vivo data requirement is not waived, but rather, FDA has determined that in vitro data is the most accurate, sensitive, and reproducible approach for establishing BE, as required under 21 CFR 320.24(a). Nonetheless, for ease of the reader, this guidance refers to either the decision to waive an in vivo BE requirement under 21 CFR 320.22 or the decision to accept in vitro BE data in accordance with 21 CFR 320.24(a) as a *biowaiver*.

With these mechanistic elements defined, PBPK modeling for biopharmaceutics applications could predict the effect of variations from the CMAs, CPPs, and CQAs on drug exposure toward the establishment of a safe space via either IVIVCs or in vivo-in vitro relationships combined with virtual BE. A *safe space* (Abend 2018) is defined by the boundaries demarcated by in vitro specifications (i.e., dissolution or, when applicable, other relevant drug product quality attributes), within which drug product variants are anticipated to be bioequivalent to one another. Less optimally, but still possible (e.g., for modified-release (MR) formulations with appropriate additional supporting data), safe space represents specifications within which drug product variants are anticipated to be bioequivalent to the pivotal clinical batch(es).[8] Building a safe space may also reduce the need for in vivo data to support regulatory assessment.[9] Although safe spaces can be used for new and generic drug products, building a safe space for a generic drug product necessitates the identification of a range of virtual dissolution profiles within which the proposed drug products are found to be bioequivalent to one another and to the reference or target drug product (e.g., via virtual BE analysis). Also, the range of virtual dissolution profiles should contain the target (i.e., biobatch or pivotal clinical batch) dissolution profile.

The implementation of PBPK analyses for biopharmaceutics applications to support drug product quality should consider a risk-based approach (e.g., Kuemmel et al. 2020) and contemplate several factors such as: (1) whether in vivo dissolution (as opposed to permeability) is the rate-limiting step toward drug absorption; (2) the in vitro and in vivo data collected to develop, verify, and validate[10] the proposed model; and (3) the complexity of the drug product formulation. For example, the use of PBPK analyses for biopharmaceutics applications to support major manufacturing changes for immediate-release (IR) drug products containing high solubility APIs generally is not warranted.[11]

[8] If a clinical investigation (i.e., any experiment other than a BA study in which a drug is administered or dispensed to, or used on, human subjects) is necessary to demonstrate the safety or effectiveness of a proposed drug product, generally this type of study goes beyond the scope of information that may be relied upon as necessary for approval in an abbreviated new drug application (see 21 CFR 314.108(a) and the guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019)). However, for ease of the reader, use of the term *clinical* in this guidance may refer to clinical investigations conducted to support the demonstration of safety or effectiveness in a drug product submitted in a new drug application, or to in vivo studies submitted to support a demonstration of BE or other requirements under section 505(j) of the Federal Food, Drug, and Cosmetic Act and FDA's implementing regulations.

[9] See for example 21 CFR 320.25(a) ("[t]he basic principle in an in vivo bioavailability study is that no unnecessary human research should be done").

[10] In the most general terms, *verification* refers to an assessment of model components, for example by examining computer codes and equations, to evaluate whether they accurately implement model assumptions; and *validation* refers to an assessment of the model performance in comparison with observed in vivo data.

[11] See the guidance for industry *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances* (August 2018).

IV. DEVELOPMENT AND EVALUATION OF PBPK MODELS FOR BIOPHARMACEUTICS APPLICATIONS

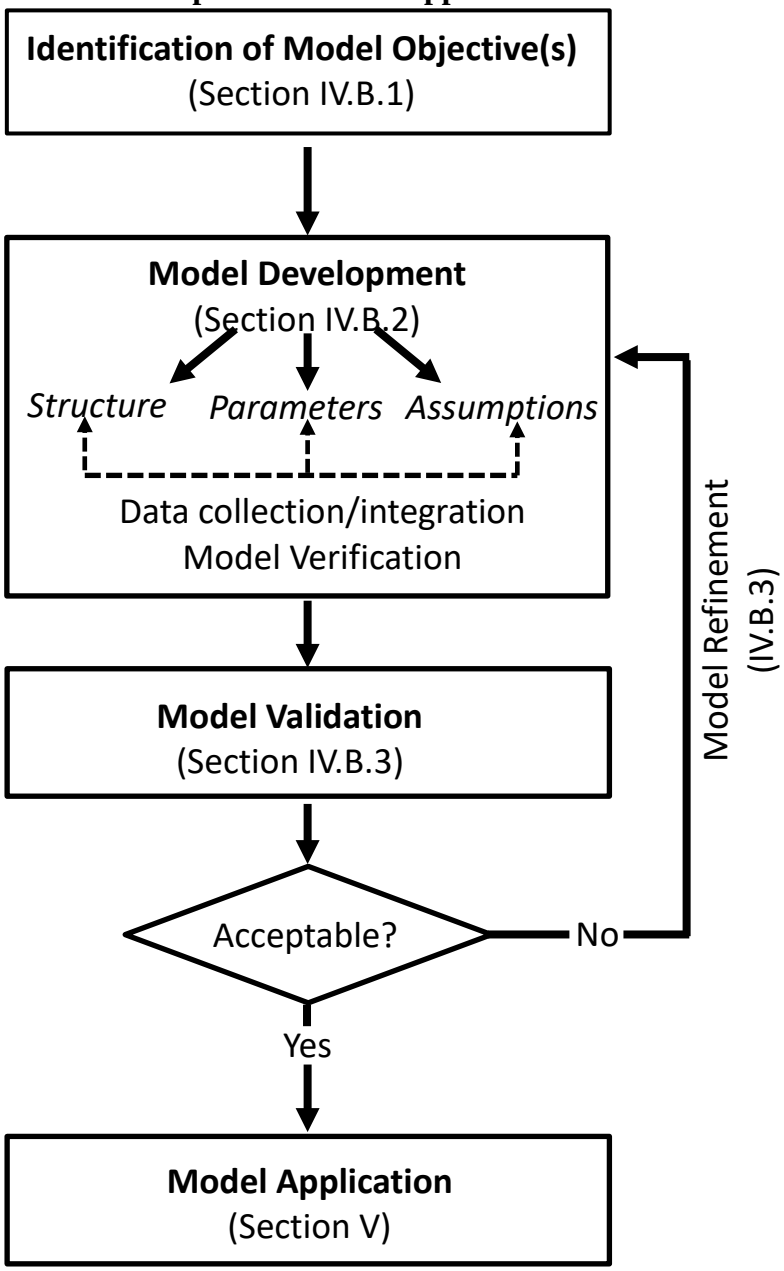
A. General Strategy

The general recommended process of developing (Zhang et al. 2011), evaluating, and applying a PBPK model for biopharmaceutics applications for an oral dosage form is presented in Figure 1 and described in this section and section V., PBPK Modeling for Biopharmaceutics Applications to Support Product Quality.

A complete study report of the modeling and simulation work using a PBPK model for biopharmaceutics applications should be submitted to FDA for evaluation and included in the electronic common technical document Module 5.3.1.3.[12]

[12] When such a model is used for other purposes, other modules may be more appropriate. For additional information, see the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (February 2020).

Figure 1. Recommended Workflow Describing Development and Evaluation of a PBPK Model for Biopharmaceutics Applications



The data needed for model development include, but are not limited to:

- Drug data comprised of drug substance physicochemical properties; formulation attributes; the drug product release mechanism; the absorption, distribution, metabolism, and excretion properties of the drug product; as well as other relevant clinical data (e.g., BA/BE or other PK data)

- System data (i.e., anatomical structure and physiological parameters) for the GI tract and other organs and/or tissues, if applicable

- Study design data (e.g., the tested drug product or formulation information, dosing regimen, and study subject population) of the in vivo studies selected for model development and validation.

B. General Considerations

The following subsections provide general considerations for model development and evaluation in supporting pharmaceutical quality.

1. Model Objective(s)

The specific drug product quality issue(s) or question(s) to be addressed by PBPK modeling for biopharmaceutics applications should be clearly described in the study report. Sponsors should provide an analysis of how the specified quality issue(s) or question(s) affect the PK performance of the drug product, the rationale for conducting the modeling and simulation, as well as any strategies undertaken to mitigate the risk of the change to PK performance. The analysis should also incorporate a description of the level of confidence in the modeling outcome based on additional data available to support the verification and/or validation of the model, and other factors, such as the model application, the therapeutic indication, and the therapeutic window of the drug. FDA will evaluate on a case-by-case basis the adequacy of the model for the intended purpose and data sufficiency for model verification and/or validation.

2. Model Development

Model development should consist of the following three general elements.

a. Model structure

The model structure should provide a mechanistic framework of drug oral absorption by representing the in vivo drug absorption process and accounting for the relevant product quality attribute(s) that affect drug dissolution and absorption. The construction of an absorption model should consider the model objective(s), as well as multiple factors affecting drug dissolution and absorption and their interactions. These factors include but are not limited to: physicochemical properties of the drug substance; formulation/process characteristics; drug release mechanism; in vivo drug dissolution process; supersaturation and precipitation processes; location and duration of absorption; drug permeation and transport pathway; and the effect of GI tract physiology on absorption. Finally, model construction should consider the supporting data and knowledge available to justify the model structure. Sponsors should also document the approaches taken to integrate quality attributes, such as dissolution, and other factors into the model.

Because the focus of the model is on in vivo dissolution and absorption, it is appropriate to combine a mechanistic absorption model with a simplified disposition model (e.g., a classic compartmental PK model or a reduced PBPK model that lumps tissue/organ compartments) for the prediction of systemic exposure following absorption. Such simplification is recommended if it does not compromise the ability to adequately describe processes governing the drug BA.

When drug disposition involves complexity (e.g., nonlinear PK, saturation of clearance pathway), we recommend an alternative approach, such as incorporating enzyme kinetics in the disposition model. Any modification to the initial model structure should include sufficient justification (e.g., the addition of structural elements may be supported by comprehensive sensitivity analyses and/or appropriate proof that clearly demonstrates the significance of the metrics of interest).

b. Model assumptions

The assumptions that underly the model structure and parameters should be clearly presented (e.g., the assumptions made upon drug disintegration, dissolution, precipitation, degradation, transport, first-pass effect, distribution, and clearance). The assumptions should be scientifically justified with supportive information and data, when available. The effect of these assumptions on model structure and/or parameter(s) should be described.

c. Model parameters

The approach taken to incorporate drug product quality attributes into the model and the selection of parameters and parameter values as model inputs should be clearly presented and scientifically justified. Selection and evaluation of CMAs (such as drug substance physicochemical properties and excipient(s) level), CPPs (such as compression force), and CQAs (such as hardness, disintegration, and in vitro dissolution) as model inputs should consider whether these attributes and parameters can affect drug in vivo dissolution and absorption.

3. Model Validation and Refinement

The predictive performance of a model should be validated for its intended purpose. Depending on the clinical risk and the intended purpose, the amount and type of data needed for model validation may vary. Independent datasets not used in model development are recommended to evaluate the predictive performance of the model. In general, for addressing pharmaceutical development and quality issues, the adequacy of the model to predict the effect of model inputs on the PK performance of the studied drug product should be demonstrated by establishing a clear rank-order relationship between in vitro testing (e.g., in vitro release/dissolution) and in vivo PK study results.

To increase confidence in the model, we strongly recommend that sponsors demonstrate the model's predictive performance based on PK data from batches exhibiting unacceptable BA, in addition to those that exhibited acceptable BA (compared to a target and/or reference product). In this context, BA would be considered unacceptable when, based on BE criteria, the 90 percent confidence interval of the test-to-reference geometric mean ratio of C_{max} and AUC fall outside the range of 80 to 125 percent. Model validation acceptance criteria should be established a priori and the criteria should be appropriate for the specified application. For instance, the acceptance criteria for a mechanistic IVIVC model to support biowaiver should comply with the criteria provided in the guidance for industry *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*.

To demonstrate model predictive performance, sponsors should provide graphical and numerical comparisons of the predicted and observed in vivo drug concentrations (e.g., in plasma) versus time profiles as well as PK parameter estimates (e.g., C_{max}, T_{max}, and AUC) and statistical analysis of those estimates (e.g., confidence intervals). Any significant deviation of the model prediction from clinical PK observation (e.g., failure to meet pre-defined model acceptance criteria) will be subject to evaluation by FDA.

When model refinement or optimization is necessary, we recommend uncertainty analyses on model structure and parameters. Such analyses can be performed by reevaluation of model assumptions and/or parameter sensitivity analysis. The model structure and/or parameters that are modified should be clearly presented and scientifically justified. When a model parameter is optimized, sponsors should provide, in addition to the scientific justification(s) and rationale, the selected initial values and range of parameters, the estimation method and optimization algorithm, and the in vitro and in vivo data used for optimization.

V. PBPK MODELING FOR BIOPHARMACEUTICS APPLICATIONS TO SUPPORT PRODUCT QUALITY

The in vivo prediction capability provided by PBPK modeling for biopharmaceutics applications allows for a wide array of uses in the pharmaceutical industry, including formulation development, biopredictive dissolution method development, clinically relevant product specifications setting, quality risk assessment, and drug product life cycle management. The implementation of PBPK modeling for biopharmaceutics applications may reduce the number of in vivo BA/BE studies (e.g., due to formulation and/or manufacturing process changes) conducted during the initial approval process, as well as support product scale-up and postapproval changes (SUPAC). The major regulatory uses of PBPK models for biopharmaceutics applications with respect to supporting product quality are presented below. For cases not discussed in this guidance, sponsors are encouraged to contact FDA.

A. Development of Clinically Relevant Dissolution Specifications (Method and Acceptance Criteria)

1. Aid in Biopredictive Dissolution Method Development

Although progress has been made with the use of biorelevant media and appropriate testing conditions to create physiologically based dissolution methods (Kostewicz et al. 2014b), the use of in vitro dissolution data to quantitatively predict drug absorption is challenging. A biopredictive dissolution method can be used to generate a dissolution profile. This profile can be used to predict systemic exposure after oral administration of solid dosage forms (Suarez-Sharp et al. 2018). The dissolution data could be effectively used as a surrogate to assess the clinically relevant effect of drug product variants, thereby streamlining drug product development.

We encourage development of biopredictive dissolution methods at the early stage of a drug product development program, especially for drug products with dissolution as the rate-limiting

step for absorption, such as MR drug products and IR drug products containing poorly soluble APIs.

With the mechanistic platform to delineate the complex mechanisms underlying drug absorption, PBPK modeling for biopharmaceutics applications can provide an estimation of a drug product's in vivo dissolution profile, based on the simulation of in vivo process of drug absorption in the GI tract. Although the estimated in vivo dissolution profile may be used as a reference, understanding of the physicochemical properties of the API and drug product quality attributes, as well as their potential effect on in vivo dissolution, is critical for the development of a biopredictive/clinically relevant dissolution method. The critical physicochemical properties of the API and drug product quality attributes include, but are not limited to: (1) its solubility in aqueous media within physiological pH range (e.g., 1 to 6.8) and/or biorelevant media (e.g., simulated gastric and intestinal fluid mimicking fasted or fed conditions); (2) saturation or supersaturation and precipitation properties; (3) mechanism of release; and (4) the in vitro dissolution characteristics in media at different pH within the physiological range.

By exploring dissolution methodologies (e.g., medium, apparatus, and hydrodynamics), an in vitro dissolution method can be developed with the intention to predict the in vivo dissolution profile of a drug product. The use of biorelevant dissolution methodology is encouraged as a starting point in the development of a biopredictive dissolution method.

To evaluate whether a dissolution method is biopredictive, sponsors should incorporate dissolution profiles generated by such method into the PBPK model and the predicted systemic exposure should be comparable (±10 percent) to the observed in vivo PK data. To evaluate the method, we recommend that sponsors use observed in vivo PK data of formulations with different release rates.

Implementation of a biopredictive method is encouraged for establishing a quality control (QC) dissolution test. If a biopredictive method is determined inappropriate to be employed for routine use (e.g., due to method complexity), an alternative dissolution method can be selected as the primary method for the QC dissolution test while the biopredictive dissolution method can be retained as an alternate testing approach for aiding in quality assessment when needed. For instance, dissolution data from a biopredictive method can supersede the primary QC dissolution testing results to support chemistry, manufacturing, and controls (CMC) changes in terms of maintaining desired in vivo performance.

2. Support Clinically Relevant Dissolution Acceptance Criteria

The term *clinically relevant dissolution acceptance criteria* is defined as a metric that can identify and reject drug product batches that are not bioequivalent to the pivotal clinical drug product (Abend et al. 2018). It often refers to the acceptance criteria set for a dissolution method to minimize the possibility of releasing batches that would have clinical performance differences. A clinically relevant dissolution acceptance criterion can be wider than that set based on the

average dissolution data of pivotal clinical batches (e.g., beyond plus or minus 10 percent variation range for an extended-release (ER) drug product).[13]

PBPK modeling for biopharmaceutics applications links in vitro dissolution to PK performance and hence supports the establishment of clinically relevant dissolution acceptance criteria. PK predictions from PBPK models for biopharmaceutics applications (e.g., virtual BE studies) based on in vitro dissolution profile(s) representing the desired limits and/or range of dissolution rate can be used to justify the clinical relevance of proposed acceptance criteria. The approach should consider comparing PK predictions based on in vitro dissolution profile(s) representing the desired dissolution limits and PK predictions based on dissolution profile of pivotal clinical batches (as a reference). Sponsors should consider the following when conducting virtual BE studies: (1) the estimated intra- and intersubject variability for PK parameters (such as C_{max} and AUC) should be representative of the observed intra- and intersubject variability; (2) the number of subjects for virtual BE trials should be justified and comparable to in vivo BE studies; and (3) the number of virtual BE trials used to estimate the probability of concluding BE should be justified.

If the outcome of the analysis meets BE acceptance criteria, the proposed dissolution acceptance criterion could support clinical relevance. For ER drug products, clinically relevant dissolution acceptance criteria preferably should be set such that all lots/batches that have dissolution profiles within the upper and lower limits of the specification are bioequivalent to one another. Less optimally, lots/batches exhibiting dissolution profiles at the upper and lower dissolution limits should be bioequivalent to the clinical/BA lots/batches or to an appropriate reference standard, but not necessarily to one another.[14] For generic drug products, the predicted PK performance corresponding to the upper and lower limits of dissolution should support that product variants are bioequivalent to each other and to the reference listed drug.

Parameter sensitivity analysis (PSA) also can be performed to evaluate the effect of the dissolution rate change on systemic exposure using validated PBPK models for biopharmaceutics applications, in support of the clinical relevance of proposed dissolution acceptance criteria.

B. Establishment of Clinically Relevant Drug Product Quality Specifications (Other Than Dissolution)

QbD is a systematic approach for pharmaceutical development and manufacturing to enhance drug product quality with more consideration of the drug product's intended use by the patients; nevertheless, it is often challenging to establish clinically relevant specifications for drug substances, excipients, in-process materials, and finished drug products. Current quality testing or control is largely based on in vitro testing/performance (including in vitro dissolution) of clinical, development, and registration batches. Although clinical data alone are often insufficient to inform appropriate drug product specifications, the overall clinical pharmacology and

[13] See the guidance for industry *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*.

[14] See the guidance for industry *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.

biopharmaceutics information gathered during drug product development can be leveraged for the development of PBPK models for biopharmaceutics applications. These models may help in establishing a desired in vitro-in vivo link, a key element in building clinical relevance for drug product quality attributes.

Provided that the quality attributes and process parameters are incorporated either directly or indirectly in the model, the effect of these attributes and parameters on in vivo dissolution and absorption can be assessed. The quality attributes can include: (1) drug substance quality attributes (e.g., particle size distribution, physical form, polymorphic form); (2) excipient quality attributes (e.g., type and/or level of release rate controlling excipient); (3) in-process quality attributes (e.g., granule particle size, coating weight gain); and (4) finished drug product attributes (e.g., disintegration). Manufacturing process parameters include, but are not limited to, coating parameters and compression force. A biopredictive dissolution profile can be used to assess the in vivo effect of the quality attributes and process parameters that cannot be directly input into the model.

Similar to setting clinically relevant dissolution acceptance criteria, clinically relevant drug product specifications for quality attributes other than dissolution can be established based on modeling predictions to ensure BE of batches within the specification limits to the pivotal clinical/BA batches (see section V.A.2., Support Clinically Relevant Dissolution Acceptance Criteria) or to the reference listed drug for generic drugs.

C. Quality Risk Assessment for Pre- and Postapproval Changes and Risk-Based Biowaivers

Sponsors can employ PBPK analyses for biopharmaceutics applications as an advanced tool for quality risk assessment and management in pharmaceutical development and drug product life cycle. Specifically, enhanced understanding can be provided by the modeling approach on how quality attributes affect clinical performance, thereby aiding in risk assessment as part of formulation and process development and the establishment of the control strategy, as well as supporting postapproval changes.

The use of PBPK analyses for biopharmaceutics applications at pre- and postapproval stages can include:

- **Preapproval Stage**

  – Establishing clinically relevant manufacturing design space and control strategy to mitigate quality risks in support of patient-centric drug product development

  – Bridging clinical batches to the to-be-marketed commercial product accounting for the CMC changes such as formulation, manufacturing process, and manufacturing site changes made during pharmaceutical development

- **Post-approval Stage**

  – Conducting risk assessment/risk classification as per SUPAC and/or the draft ICH guidances for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management: Core Guideline* (November 2017) and *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management: Annex* (November 2017)[15] on postapproval CMC changes such as formulation, manufacturing process, and manufacturing site changes

  – Supporting biowaivers for postapproval changes

Risk assessment can be performed using the same approach as illustrated in section V.A. and B. in setting clinically relevant drug product specifications. In this regard, model prediction(s) or PSA results may be used to support high-impact CMC changes that may otherwise need an in vivo BE study per the guidances for industry *Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* and *SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (September 1997). FDA may grant a biowaiver request supported by PBPK modeling for biopharmaceutics applications after evaluation of the outcome of the risk assessment, the level of impact of the proposed change, and the totality of the provided information.

[15] When final, these guidances will represent the FDA's current thinking on these topics.

GLOSSARY

Biopharmaceutics: The study of the physical and chemical properties of a drug, its dosage form, and formulation, as related to the onset, duration, and intensity of drug action.

Biopredictive dissolution method: A set of testing conditions for which in vitro dissolution profiles are capable of predicting PK profiles. These are typically based on classical or mechanistic IVIVC.

Biorelevant dissolution method: A set of testing conditions (e.g., media and hydrodynamics) for monitoring in vitro dissolution designed to closely mimic a relevant biological fluid and a physiological environment.

Clinically relevant dissolution specification: A specification that takes into consideration the clinical effect of variations in dissolution ensuring a consistent safety and efficacy profile.

Critical process parameter (CPP): A process parameter whose variability has an effect on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality.[16]

Critical quality attribute (CQA): A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired drug product quality.[17] CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials), and drug product.

Design space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to ensure quality. Working within the design space is not considered to be a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process. Design space is proposed by the sponsor and is subject to regulatory assessment and approval.[18]

In vitro/in vivo correlation (IVIVC): A predictive mathematical model describing the relationship between an in vitro property of an ER dosage form (usually the rate or extent of drug dissolution or release) and a relevant in vivo response (e.g., plasma drug concentration or amount of drug absorbed).[19]

In vitro-in vivo relationship: A qualitative rank-order relationship between a relevant in vivo response and in vitro release profiles.

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[16] See ICH Q8(R2).

[17] Ibid.

[18] Ibid.

[19] See the guidance for industry *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*.

Parameter sensitivity analysis (PSA): A series of analyses targeting the same estimand, with differing assumptions to explore the robustness of inferences from the main estimator to deviations from its underlying modeling assumptions and limitations in the data.[20]

Physiologically based pharmacokinetic (PBPK) analysis: An analysis using models and simulations that combine physiology, population, and drug characteristics to mechanistically describe the PK and/or pharmacodynamic behaviors of a drug product.[21]

Risk assessment: A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.[22]

Safe space: Boundaries defined by in vitro specifications, such as dissolution or other relevant drug product quality attributes, within which drug product variants are anticipated to be bioequivalent to one another.

[20] See the draft ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (June 2017). When final, this guidance will represent the FDA's current thinking on this topic.

[21] See the guidance for industry *Physiologically Based Pharmacokinetic Analyses — Format and Content*.

[22] See the ICH guidance for industry *Q9 Quality Risk Management* (June 2006).

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