Mechanistic Modeling of Complex Injectables: Recommendations to Navigate Regulatory Challenges

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 4: Scientific Challenges and Advancements of Long-Acting Injectables (LAIs)

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Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Learning Objectives

- Utility of mechanistic modeling in the development of complex injectables
- Key considerations for model-based alternative bioequivalence (BE) approach
- Recommendations to Navigate Regulatory Challenges: Discussion with hypothetical scenarios
- Interaction with the agency: Key considerations in preparing pre-ANDA meeting package

Examples of Complex Injectables

Long-acting injectable (LAI) suspension

- INVEGA SUSTENNA® (paliperidone palmitate extended-release injectable suspension)
- DEPO-PROVERA® (medroxyprogesterone acetate injectable suspension)

Polymer based implants and in-situ forming implants

- ZOLADEX® (goserelin acetate) : poly(lactic-co-glycolic acid) (PLGA)-based implant
- ELIGARD® (leuprolide acetate) : in situ forming PLGA implant

Lipid based nanoparticles

- DOXIL® (doxorubicin hydrochloride) liposome for injection
- VYXEOS® (daunorubicin and cytarabine) liposome for injection

IV colloidal solution or nanoparticles suspension

- ABRAXANE® (paclitaxel protein-bound particles for injectable suspension)
- FYARRO® (sirolimus protein-bound particles for injectable suspension)
- Iron carbohydrate colloid drug products: INFED®, FERRLECIT®, VENOFER®, VELPHORO®

Development of Complex Injectables: Challenges With In Vivo BE Study

Development of complex injectables is often challenging. Many complex injectables including LAIs have no/limited number of generic drug products.

- Increased variation in pharmacokinetic (PK) parameters; but source of variability remains vague
- Challenges in patient recruitment as healthy subjects are often not recommended
- High dropout rate as PK studies are subjected to longer time periods
- Often not practical to perform a single-dose crossover BE study

Utility of Mechanistic Modeling in the Development of Complex Injectables

Mechanistic physiologically-based pharmacokinetic (PBPK) modeling has the potential to save time and resources in the development of generic complex injectable drug products

- Support product approval via a virtual bioequivalence (VBE) study
- Understand the effect of key formulation attributes on systemic PK exposure
  - — Effect of particle size, surface morphology of API, pH and viscosity of formulation
  - — Define safe space between test and reference drug products
- Explain source of PK variability
  - — Can integrate the interaction of API with physiology (e.g., local immune cells)
  - — Account for in vivo aggregation of particles at injection depot (e.g., IM/SC inj)
- Establish in vitro-in vivo correlation (IVIVC) by incorporating in vitro release data
- Extrapolate IVIVC from animal model to human subjects by accounting species specific physiological difference

Key Considerations for Model-based Alternative BE Approach

1 Model Development

- Model should describe the relevant physiology, integrate key formulation attributes, and account the interplay between formulation attributes and physiological parameters

2 Primary Model Verification

- To ensure predictive ability of the primary PBPK model, e.g., by changing key formulation attributes such as particle size in intentionally manufactured variant formulations

3 Secondary Model Verification

- To ensure creditability of general PBPK model structure by verifying the model against wide range of drug products administered through same route

4 Application of Model

- Conduct virtual BE (VBE) study
- Establish mechanistic IVIVC
- Explain source of PK variability

Applicants may consider reading the white paper describing the development of dermal PBPK model and may utilize relevant suggestions and ideas in the development and verification of complex injectable PBPK model.

Hypothetical Drug Developmental Scenarios

Example-1: LAI Suspension for IM Use

Hypothetical product-specific guidance (PSG) recommends: In vivo BE study (either parallel or crossover BE study at steady-state) with PK endpoint in patients who are already receiving a stable regimen

Hypothetical query from applicant

PSGs for azacitidine and triamcinolone acetonide injectable suspension recommend in vitro approach to establish BE. Can in vitro characterization-based approach be explored for this LAI suspension?

Hypothetical response from FDA

The recommendations and rationale are specific to a drug product, and it is generally not sufficient or appropriate to justify a proposed approach based on the PSG recommendations for a different drug product.

Neither azacitidine injection nor triamcinolone acetonide injectable suspension is intended for long-term use in patients. Potential safety and efficacy risks associated with this LAI suspension are much higher compared to other similar drug products.

Example-1 : LAI Suspension for IM Use

Hypothetical question in pre-ANDA space:

Innovator company for this LAI suspension has established IVIVC and some relevant information is available in the NDA review. A generic drug development company used this information (i.e., IVIVC established by the innovator company) to develop a PBPK-model based mechanistic in vitro-in vivo relationship (IVIVR) and the IVIVR was based on data of only one formulation that has intermediate release rate.

The generic drug development company proposed to predict the bioavailability of the test and reference drug products by utilizing PBPK modeling and IVIVR and asked for Agency's feedback on their proposal.

Hypothetical response from FDA

- IVIVC is generally established by knowing the manufacturing history and intentionally formulating batches with various release rates such as slow, medium, fast
- NDA applicant established IVIVC cannot be adapted by generic applicants for supporting regulatory approval
- Generic applicants may use this knowledge (IVIVC developed by the NDA applicant) as a starting point to develop the IVIVC for their own test product

Example-1 : LAI Suspension for IM Use

Relevant question:

Can animal models be used to establish IVIVC of the test formulation?

Hypothetical response from FDA:

- If generic applicant intends to use IVIVC to support the approval of their test product, only human data should be applied for regulatory consideration of an IVIVC. Animal studies cannot be used in lieu of human studies for BE determination.

- Results from animal studies can only be used for product development, such as supporting identification of the critical quality attributes (CQAs) of a drug product or justifying the use of a proposed alternative approach.

Example-2: Colloidal Solution or Nanoparticle Suspension

Hypothetical PSG recommendation

Both in vivo BE study with PK endpoint and in vitro study (particle size distribution and physicochemical characterization)

Hypothetical question from applicant

Can in vitro characterization-based approach be explored for this drug product since API of this drug product dissociated from excipient upon intravenous administration?

Hypothetical response from FDA

Variation in manufacturing conditions for nanoparticles drug products (i.e., colloidal solution or nanoparticle suspension) may result some differences in surface chemistry of API which may influence plasma protein binding of the API and thus could lead to difference in systemic drug disposition of API

Example-2: Colloidal Solution or Nanoparticle Suspension

Hypothetical question utilizing modeling approach:

Can the data from tissue distribution studies in mice with the test and reference product be used to develop a PBPK model? Can the mouse model be extrapolated to human and the model be used conduct VBE study to establish BE?

Hypothetical response:

API of nanoparticles drug products can be substrate of transport proteins and cytochrome 450 enzymes. There can be certain differences in the disposition characteristics of API between mice and humans.

- Human orthologs of certain transport proteins are absent in mice
- Major metabolite formed in human could be different than that formed in animal model
- Plasma protein binding of API in human and mice may differ substantially
- API may eliminate substantially faster in one species compared to other

Example-2: Colloidal Solution or Nanoparticle Suspension

Hypothetical response from FDA (continued…)

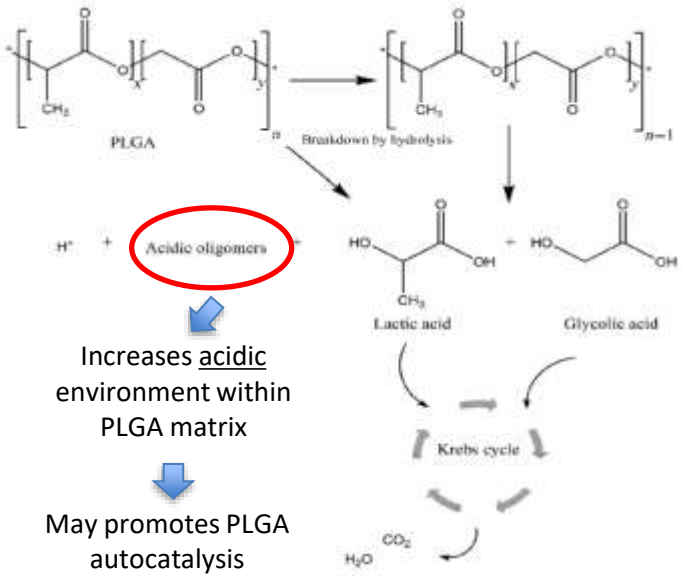
Extrapolation of mouse PBPK model to human PBPK model is not straight forward process (e.g., not simple allometric scaling of clearance process). Development of **mechanistic model** with the consideration of species-specific differences in physiology may be considered.

Additionally, proposed plan should -

- have sufficient description regarding the PBPK model development and predictive ability of the model for the drug product
- discuss how the formulation attributes of the test and reference products would be incorporated into the model
- discuss the plan on estimating potential formulation difference and VBE analysis (reasonable consideration of inter- or intra-subject variability, number of subjects, Type I and II error analysis)

Example-3: PLGA-based implant of API

- **Molar ratio of lactic acid and glycolic acid in PLGA polymer, average molecular weight of PLGA are assumed to be critical in the degradation of PLGA and subsequent drug release from PLGA matrix**
  - Degradation of PLGA occurs by the hydrolytic cleavage of the backbone ester linkages and first broken down to small oligomers and then to monomers
  - Autocatalysis may cause faster degradation at the center of the PLGA matrix than on the surface since acidic biproducts are neutralized more rapidly on the surface



- **Many PLGA based drug products show distinct PK profile (e.g., primary and secondary peak) which is assumed due to complex interplay between formulation CQAs, implant specific properties, physiology etc.**

Example-3: PLGA-based implant of API

Hypothetical PSG recommendation

Single dose parallel in vivo BE study in patients with PK endpoints

Challenges with in vivo studies:

- High inter-subject variability
- Requires large number of subjects to achieve adequate power for BE study
- Recruitment of specific patient population is difficult
- Cross-over study poses some challenges as the drug may potentially show carryover between subsequent periods due to the long-acting nature of the drug product

Mechanistic modeling of PLGA-based implant may overcome the challenges associated with the in vivo BE study

Example-3: PLGA-based implant of API

Hypothetical question in pre-ANDA space:

A generic drug development company proposed to demonstrate virtual BE by applying PBPK modeling and simulation that will be informed by an abbreviated in vivo parallel BE study (i.e., underpower BE study) with the reference and test formulations to generate virtual subjects for the VBE study. The generic drug development company asked for the Agency's feedback on the mechanistic PBPK model development and VBE analysis plan.

Hypothetical response from FDA:

A mechanistic PBPK model can be utilized for demonstrating VBE given that –

- Model adequately describes the drug release mechanism
- Model is informed with
  - Formulation CQAs such as PLGA molar ratio, molecular weight of PLGA
  - API specific physicochemical properties such as intrinsic solubility, hydrophobicity of API
  - Implant specific properties such as size and shape of the implant, drug loading, porosity etc.
- The primary PBPK model is adequately verified for its predictive ability
  - By intentionally manufacturing variant formulations with PLGA molar ratio, molecular weight, drug loading, porosity, etc.
- The PBPK model is verified against wide range of similar drug products to ensure creditability of the model
- The plan to identify potential formulation difference and VBE analysis plan (reasonable consideration of inter- or intra-subject variability, number of subjects, Type I error analysis) is adequately described

Interaction with the Agency for Model-based Alternative BE approach

Early interaction with FDA (e.g., pre-ANDA product development meeting) is encouraged. The modeling does not have to be completed but it should be in a sufficient state of development to allow for scientific discussion of specific aspects of the model.

Key considerations in preparing pre-ANDA meeting package:

- Clearly state the purpose of the modeling approach (i.e., supporting IVIVC vs. VBE study)
  - Any model assumption that has the potential to mitigate any actual differences between the two formulations would be more suspect and need a greater level of justification
- When the model is proposed for establishing VBE, describe your plan adequately regarding how potential formulation difference would be estimated
- Clearly state the study design and data analysis plan for VBE
  - Incorporation of inter- or intra-subject variability is often challenging. However, reasonable assumption on variability with proper justification should be discussed
- Provide considerations for how the VBE approach ensures adequate Type I error by demonstrating the sensitivity of the approach to detect non-BE situations

Take Home Message

- Mechanistic PBPK modeling has the potential to overcoming challenges associated with in vivo BE study and thereby can save time and resources in generic drug development
- Animal studies cannot be used in lieu of human studies for BE determination. However, generic applicants may use the results of animal studies for product development, such as identifying CQAs or supporting justification for the proposed alternative approach.
- NDA applicant established IVIVC cannot be adapted by generic applicants for supporting regulatory approval. Generic applicants may use this knowledge (IVIVC developed by the NDA applicant) as a starting point to develop the (mechanistic) IVIVC for their own test product.
- Early interaction with Agency (e.g., pre-ANDA product development meeting) is encouraged for model based alternative BE approach to get Agency's feedback on the proposed approach
  - Clearly state the purpose of the modeling approach
  - Provide sufficient information on model development process
  - Provide sufficient evidence and/or plan on the model verification process
  - Provide relevant description or analysis for BE (e.g., VBE) demonstration

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Challenge Question #1

How can mechanistic modeling be utilized in the development of generic complex injectables?

Mechanistic modeling of complex injectables-

A. Can help in overcoming challenges associated with in vivo BE study

B. Can help in understanding the effect of key formulation attributes on systemic PK exposure

C. Can help in explaining the source of PK variability (e.g., by accounting the interaction of API with immune cells, in vivo aggregation of particles at injection depot)

D. Can help in drug approval process via virtual bioequivalence (VBE) study

E. All of the above

Challenge Question #2

What consideration(s) should be taken into account during the preparation of pre-ANDA meeting package when model based alternative BE approach is proposed?

A. Clearly state the purpose of the modeling approach and provide relevant description or analysis

B. Provide sufficient information on model development process

C. More justification is needed for model assumption that has the potential to mitigate actual differences between the two formulations

D. Provide sufficient evidence and/or plan on the model verification process

E. All of the above


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