Model Integrated Bioequivalence Approaches for Long Acting Injectables

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Model Based BE for LAI

Plan

- Definitions
  - Model-Based BE
  - LAI
- When to use
- Principles of Model Based BE
  - Types of Model-Based BE & PPK algorithms
  - Types of clinical design (parallel vs. crossover)
  - Incomplete vs. complete sample size
- Model-Based BE
  - PK characterization of LAI with Population PK (PPK)
  - Plan, differentiation, and validation of the approach (alpha error, power)
  - Meet FDA through Product Development Meeting
  - Conduct pivotal clinical study followed by proposed Model-based analysis

Model Based BE for LAI

Long-Acting Injectables (LAI)

Standard Approaches (90% power, 0.95 T/R) vs. Model-Based

Product	BE IPG	STD approach	Length (sample size)	Model-based (sample size)
Invega Sustenna	Yes	SS parallel Patients	~8 months (n~180/group)	2-4 doses Crossover (RT/TR or RTRT/TRTR)
		SS cross Patients	8 + 8 WO + 8= 24 months	
Invega Trinza	Yes (08/21)	SS parallel Patients	18 months minimum	
		SS cross Patients	18 + 18 + 18 = 54 months	

Note: Feasible / Not really Feasible

Model Based BE for LAI

Introduction - Definitions

What is a *Model Based BE?*

When one uses a model for the pivotal assessment

- 1995 Skin blanching guidance
- IVIVC
- Dose-Scale analyses

STATE OF THE ART

Table 2 Situations in which model-based bioequivalence assessment should be advantageous or prioritized

Scenarios	Examples	Advantages
Drugs with complex PKs that may violate assumptions of NCPT analyses: · Nonlinear PK · Not eliminated from the sampling compartment · Endogenous homeostatic feedback mechanism	· Drugs with nonlinear PK and/or those that are not eliminated by renal excretion or hepatic metabolism (e.g., iron products)[67] · Endogenous products with an unstable baseline due to homeostatic feedback mechanisms (e.g., Levothyroxine in healthy volunteers) or with high baseline values relative to the observed C_{max}	Model directly incorporates and addresses characteristics that are not related to the formulation performances allowing a more robust assessment of BE. In the case of iron products, this approach seems to require a much lower sample size compared to NCPT analysis[67]
Biosimilars	· Peg-filgrastim · Rituximab · Adalimumab	· Model can help identify PK differences that could be due to the formulation and/or to the biologic. · Model should allow better interchangeability assessment[71]
Study population does not allow extensive blood samples to be collected	· Pediatric studies · Patient studies[66]	Allows study to include fewer samples, and at various times after dose administration (do not need to be either after single dose or at steady state)
Systemic drug exposure not detectable	· Extremely low bioavailability drug and/or analytical limitations (e.g., alendronate sodium in the past)[59,60] · Product for which PD parameters can be obtained without corresponding PK data[60,64]	Differences in formulation performances can be extracted from another medium (e.g., urine) or with PD measures only[60]
Topical, locally acting dermatological products besides corticosteroids	· Skin stripping data[65]	Comparison of rate and extent of exposure at the site of activity (skin) can be obtained, circumventing the need for large and indiscriminative equivalence studies with clinical end points
Complex modified release products	· Long-acting modified release products, including injectables · Multiphasic modified release products · Transdermal formulations (e.g., nitroglycerin)[57,58]	The diverse release mechanisms can be compared between two formulations, robustly differentiating them from behavior that is drug related
Situations where sample size needed to pass equivalence limits (e.g., 80–125) would be unfeasible for an ethical, financial and/or technical reason	· Clinical equivalence study with variability in clinical end point response that is too high	Using smaller-sized clinical study(ies), simulations of studies with different and greater sample sizes could be used for equivalence assessment

BE, bioequivalence; C_{max}, peak plasma concentration; NCPT, noncompartmental; PD, pharmacodynamic; PK, pharmacokinetic.

scenarios proposed in **Table 2**, model-based approaches have already shown their usefulness.[60]

HOW TO ASSESS BIOEQUIVALENCE USING MODEL-BASED APPROACHES?

The essence of this approach, when it applies to drugs that act systemically, consists in the development of a population PK model that simultaneously fits data from both test and reference products. Model parameters related to formulation performances, such as absorption rate constants (Ka_{test} and Ka_{ref}) and a relative bioavailability parameter (F_{rel}), would be fitted to allow differences in rate and extent of exposure, whereas all other model parameters describing the drug's systemic processes such as distribution and elimination (volumes of distribution and clearances) would be identical for both formulations. The model parameters that are indicative of formulation performances can then be compared statistically in a manner analogous to the comparison of the AUC and C_{max} metrics with ln-transformed T/R ratios and 90% CIs. Finally, as mentioned earlier, the model-based results also in terms of fitted or predicted C_{max} and AUCs can then be subjected to the same statistical comparisons.

The use of K_a as a potential end point for assessing bioequivalence is interesting because it is purely representative of the absorption rate. In contrast, as explained previously, C_{max} derived by NCPT analysis is a function of various processes, therefore, it does not only reflect rate. However, the K_a on its own may be a parameter that is too discriminative for bioequivalence comparisons. **Table 3** presents potential metrics for bioequivalence that could be used for different types of systemically acting products and compares them to metrics that could be determined by NCPT methods. As previously noted, K_a can sometimes be too discriminative as a bioequivalence metric, and it should, therefore, be considered in conjunction with the fitted or predicted C_{max}.

Figure 2 illustrates potential bioequivalence metrics for different types of products and for various approaches. Parameters that could be compared to assess bioequivalence are those in red, and parameters in green represent product-specific parameters that may or may not be different for each formulation.

Ref.: Seng Yue C, Ozdin D, Selber-Hnatiw S, Ducharme MP. Clin Pharmacol Ther 2019;105(2):350-362.

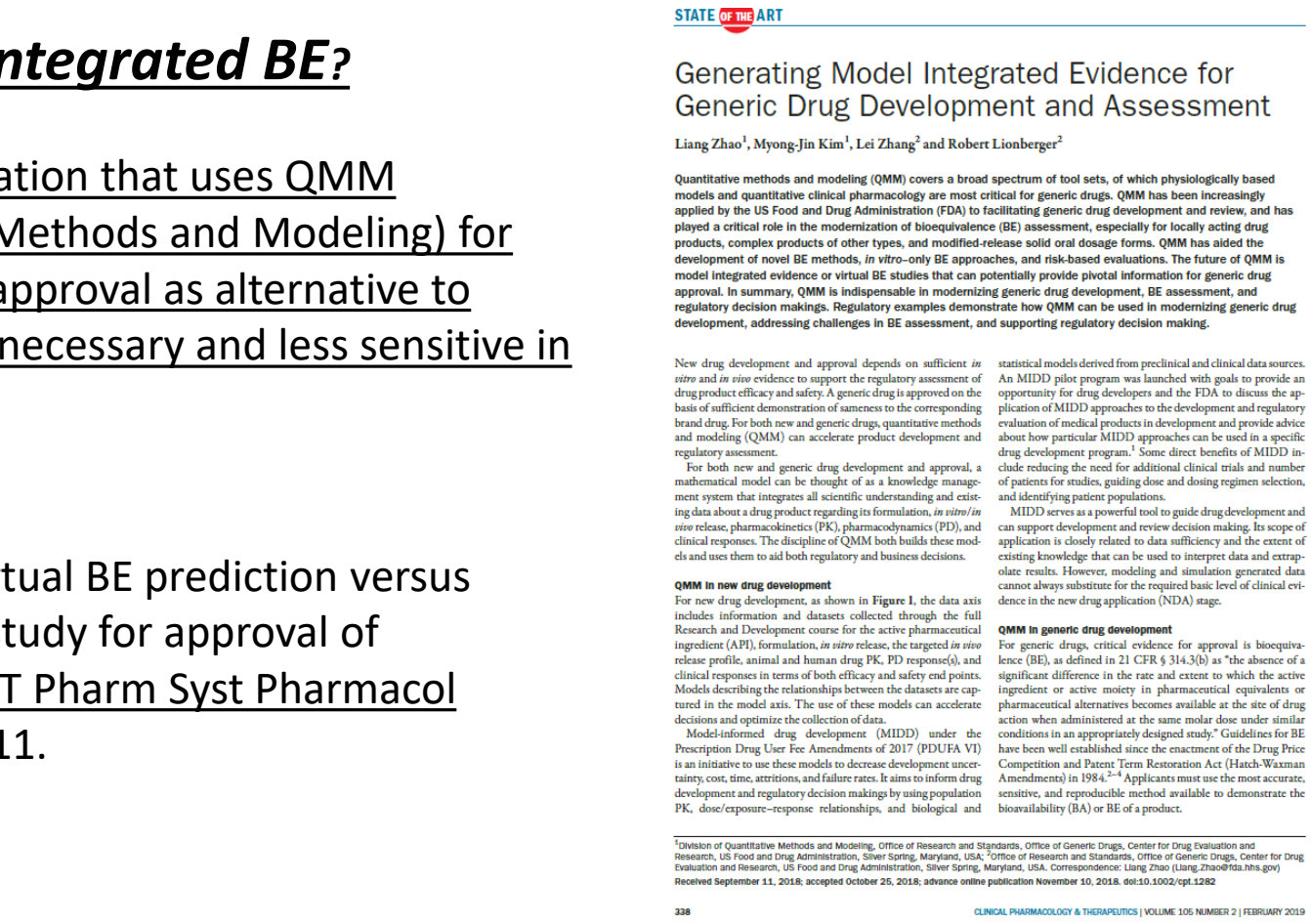
Model Based BE for LAI

Introduction - Definitions

What is a *Model Integrated BE?*

Pivotal information that uses QMM (Quantitative Methods and Modeling) for Generic Drug approval as alternative to conducting unnecessary and less sensitive in vivo studies

Example: PBPK virtual BE prediction versus clinical endpoint study for approval of Diclofenac gel (CPT Pharm Syst Pharmacol 2021;10(5):399-411.



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Generating Model Integrated Evidence for Generic Drug Development and Assessment

Liang Zhao[1], Myong-Jin Kim[1], Lei Zhang[2] and Robert Lionberger[2]

Quantitative methods and modeling (QMM) covers a broad spectrum of tool sets, of which physiologically based models and quantitative clinical pharmacology are most critical for generic drugs. QMM has been increasingly applied by the US Food and Drug Administration (FDA) to facilitating generic drug development and review, and has played a critical role in the modernization of bioequivalence (BE) assessment, especially for locally acting drug products, complex products of other types, and modified-release solid oral dosage forms. QMM has aided the development of novel BE methods, *in vitro*–only BE approaches, and risk-based evaluations. The future of QMM is model integrated evidence or virtual BE studies that can potentially provide pivotal information for generic drug approval. In summary, QMM is indispensable in modernizing generic drug development, BE assessment, and regulatory decision makings. Regulatory examples demonstrate how QMM can be used in modernizing generic drug development, addressing challenges in BE assessment, and supporting regulatory decision making.

New drug development and approval depends on sufficient *in vitro* and *in vivo* evidence to support the regulatory assessment of drug product efficacy and safety. A generic drug is approved on the basis of sufficient demonstration of sameness to the corresponding brand drug. For both new and generic drugs, quantitative methods and modeling (QMM) can accelerate product development and regulatory assessment.

For both new and generic drug development and approval, a mathematical model can be thought of as a knowledge management system that integrates all scientific understanding and existing data about a drug product regarding its formulation, *in vitro*/*in vivo* release, pharmacokinetics (PK), pharmacodynamics (PD), and clinical responses. The discipline of QMM both builds these models and uses them to aid both regulatory and business decisions.

QMM in new drug development

For new drug development, as shown in **Figure 1**, the data axis includes information and datasets collected through the full Research and Development course for the active pharmaceutical ingredient (API), formulation, *in vitro* release, the targeted *in vivo* release profile, animal and human drug PK, PD response(s), and clinical responses in terms of both efficacy and safety end points. Models describing the relationships between the datasets are captured in the model axis. The use of these models can accelerate decisions and optimize the collection of data.

Model-informed drug development (MIDD) under the Prescription Drug User Fee Amendments of 2017 (PDUFA VI) is an initiative to use these models to decrease development uncertainty, cost, time, attritions, and failure rates. It aims to inform drug development and regulatory decision makings by using population PK, dose/exposure–response relationships, and biological and statistical models derived from preclinical and clinical data sources. An MIDD pilot program was launched with goals to provide an opportunity for drug developers and the FDA to discuss the application of MIDD approaches to the development and regulatory evaluation of medical products in development and provide advice about how particular MIDD approaches can be used in a specific drug development program.[1] Some direct benefits of MIDD include reducing the need for additional clinical trials and number of patients for studies, guiding dose and dosing regimen selection, and identifying patient populations.

MIDD serves as a powerful tool to guide drug development and can support development and review decision making. Its scope of application is closely related to data sufficiency and the extent of existing knowledge that can be used to interpret data and extrapolate results. However, modeling and simulation generated data cannot always substitute for the required basic level of clinical evidence in the new drug application (NDA) stage.

QMM in generic drug development

For generic drugs, critical evidence for approval is bioequivalence (BE), as defined in 21 CFR § 314.3(b) as "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." Guidelines for BE have been well established since the enactment of the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) in 1984.[2–4] Applicants must use the most accurate, sensitive, and reproducible method available to demonstrate the bioavailability (BA) or BE of a product.

[1]Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA; [2]Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA. Correspondence: Liang Zhao (Liang.Zhao@fda.hhs.gov)

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Ref.: Zhao L, Myong-Jin K, Zhang L, Lionberger R. Clin Pharmacol Ther 2019;105(2):338-349.

Model Based BE for LAI

When to use Model Based Approaches?

Beneficial versus Standard Approaches

- Model-Based renders establishing BE feasible from a clinical point of view
  - LAI that would necessitate a study lasting many years versus a few months
  - Study interrupted or becoming unfeasible because of COVID19 pandemic restrictions
- Model-Based renders establishing BE feasible from a technical point of view
  - Standard approach is not robust enough (not discriminative/High alpha error/Low power)
- Model-Based renders establishing BE feasible from a monetary standpoint (important to make sure that generic products are cost effective)
  - Example of PBPK VBE for diclofenac gel instead of Clinical Endpoint study

Model Based BE for LAI

Long-Acting Injectables (LAI)

Injectable products that are modified release, and that liberate the Active Ingredient over a very long time period

Active Ingredient	Elimination half-life	Normal dosing interval	LAI trade name	LAI dosing interval
Aripiprazole	75h	QD	Abilify Maintena	1 month
			Aristada	2 months
Progesterone	20-30h (IM)	QD	Depo-Provera	3 months
Prednisolone	3-4h	QD	Depo Medrol	Not clear (lasts 1-2wks?)
Olanzapine	33h		Zyprexa Relprevv	Q 2-4wks
Paliperidone	23h	QD	Invega Sustenna	Q 4wks
			Invega Trinza	Q 12wks
Risperidone	3h (EM) 19h (PM)	BID - QD	Risperdal Consta	Q 2wks

Model Based BE for LAI

Long-Acting Injectables (LAI)

Standard Approaches (90% power, 0.95 T/R) vs. Model-Based

Product	BE IPG	STD approach	Min Length (sample size)	Ex. Of Model-based (sample size)
Abilify Maintena	Yes	SS parallel Patients	~7 months (n~180/group)	2-4-6-8 doses Crossover (RT/TR or RTRT/TRTR) Finish n>24 with 4w SABE Duration: 2 to 8 months
		SS cross Patients	7 + 7 WO + 7= 21 months	
Depo Provera	Yes	SD parallel Post Menop.	4 months (n~145/group)	Not needed
		SS cross Patients	18 + 18 + 18 = 54 months	

Note: Feasible / Not really Feasible

Two main types of Model-Based BE

1) Virtual BE (e.g., 1000+ BE studies simulated with simulated patients)
    1) Need a PPK model that is validated for this purpose
    2) In practice, very difficult to validate. A model is never perfect, and often can be very far from being perfect for these complicated drug products.
    3) Clinical sample size can be smaller than the ones needed for 80/90% power

2) Continuation "in silico" of dosing to the exact same patients for which we have clinical data, using a standard, conservative and conventional design
    1) BE based on actual clinical patient data
    2) Validation is simpler as one needs to only show that the individual fits are appropriate, not the population part of the model that would be used for simulations
    3) Needs a clinical sample size that will result in 80 or 90% power

Two main types of Population PK (PPK) analyses for Model-Based BE

1) FOCE/FOCEI (NONMEM®)
    1) Most experienced tool for PPK
    2) Many useful add-on tools exist to simplify and automate analyses (e.g., Xpose®, Wings®)
    3) Limitations on the complexity of the model that can be coded
    4) Convergence issues, NM-Tran translation issues

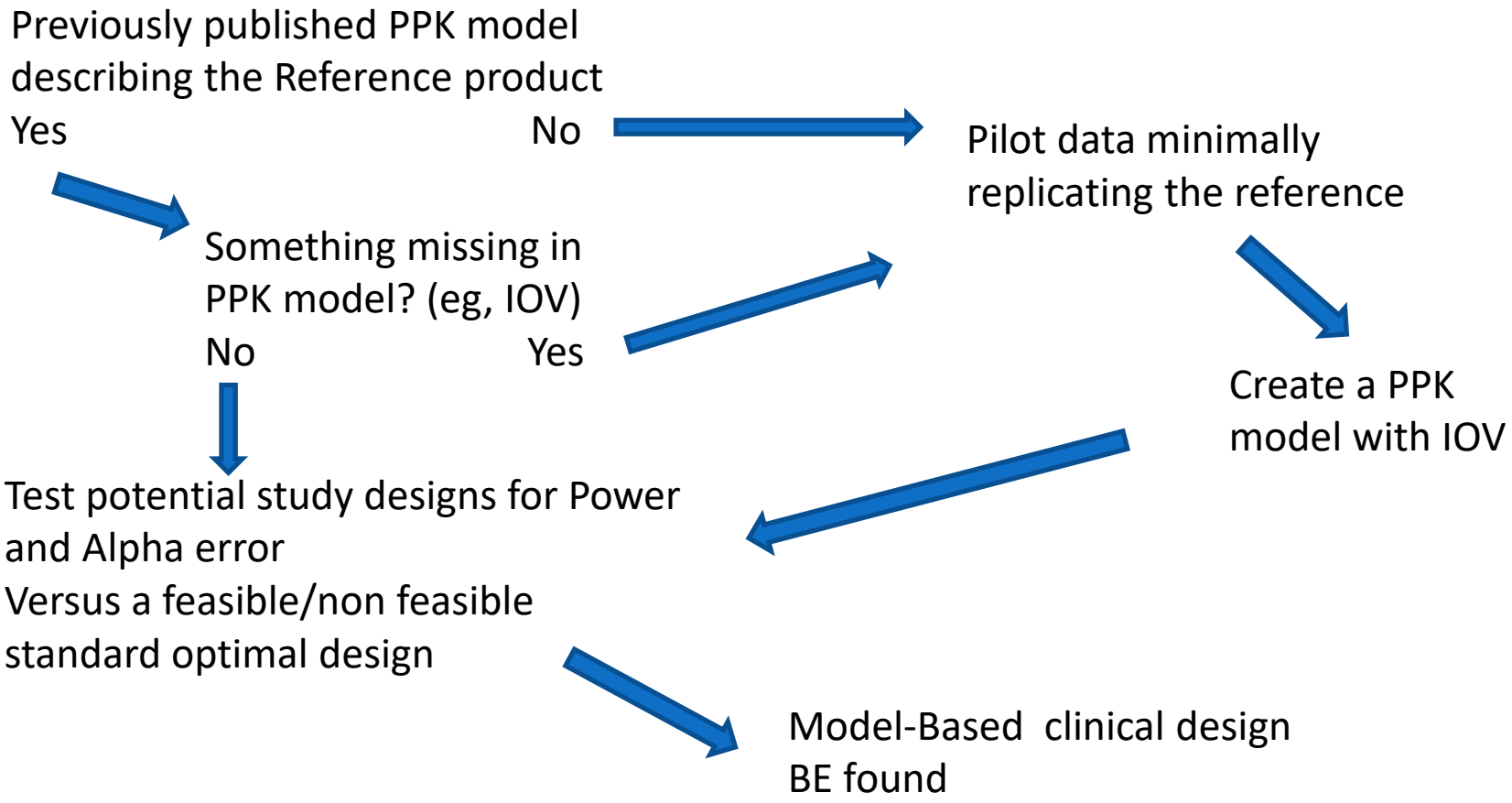
2) EM (MLEM, ADAPT5®)
    1) No limitations regarding complexity of model
    2) Robust results
    3) Slower run time, convergence criteria can be misunderstood, few add-ons
    4) Similar algorithms can also be found in Certara NLME, Monolix, and NONMEM tools among others

Model Based BE for LAI

Principles of Model-Based BE

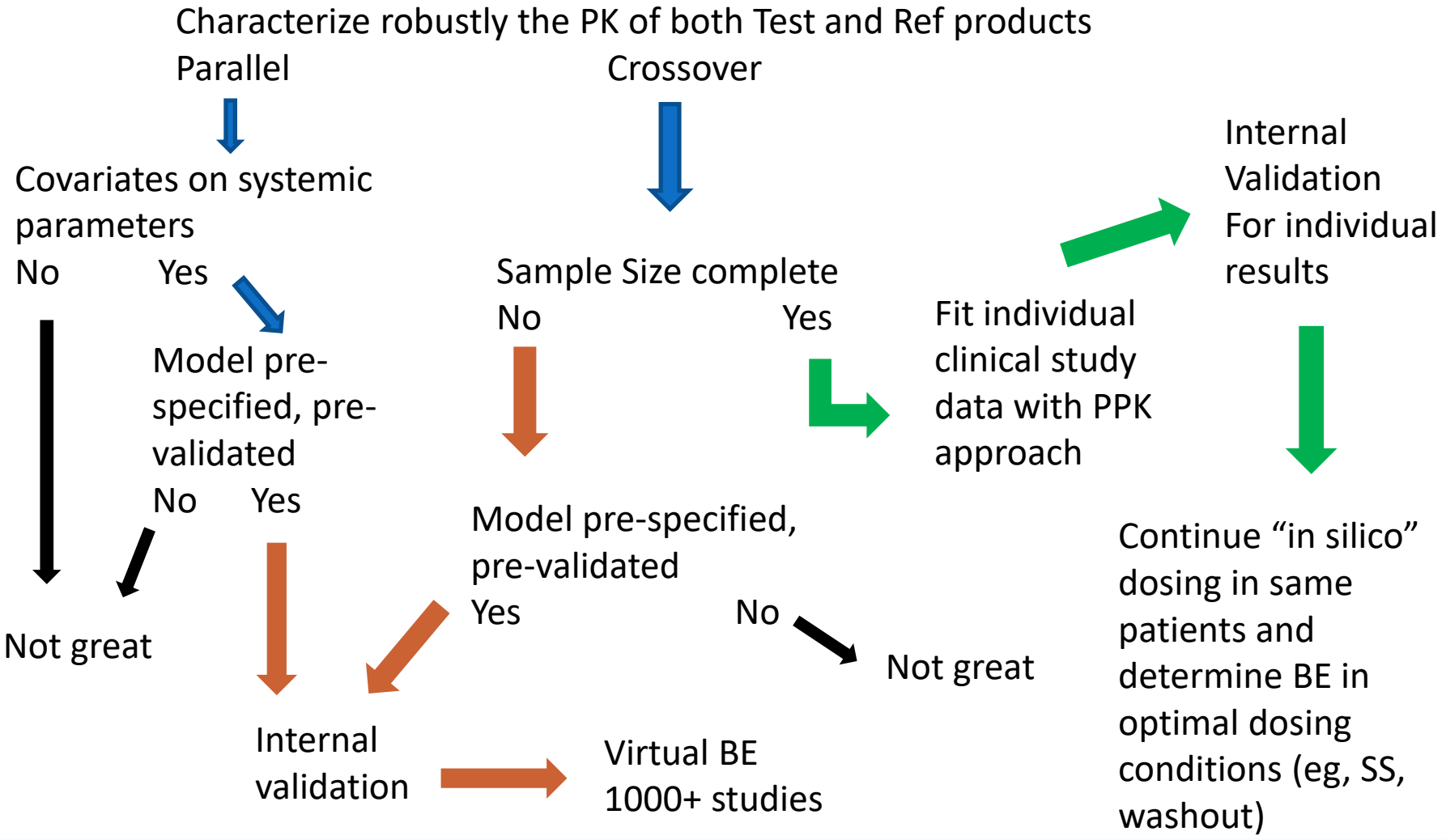
1) A Model based clinical design can be:
    1) Parallel or Crossover
    2) Limited sample size or complete sample size
2) Finding an alternative Model-Based study design?
    1) Need a PPK model
    2) Validate model
    3) Compare multiple model-based designs to a standard conventional (but often unfeasible) design in terms of power and alpha errors
    4) Propose Model-based clinical design
3) Submit proposal with future PK Analysis Plans to FDA as part of Product Development Meeting
4) Conduct the pivotal clinical study, the model-based BE analysis and submit

How to Find an alternative Model-Based study design?



Model Based BE for LAI

Principles of Model-Based BE



Model Based BE for LAI

Conclusion

- A major advance for establishing BE of complicated products such as LAI
- Different types are available
- Most robust and reliable arguably use:
  - Crossover design
  - Complete sample size
  - Continuation of patients “in silico” to whichever study design is preferred to establish BE

•Model-Based BE are also invaluable for many other types of products for which establishing BE through standard approaches may be unfeasible.

LEARN AND CONFIRM

Thank you!

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