Model-Integrated Evidence for Generic Drug Development

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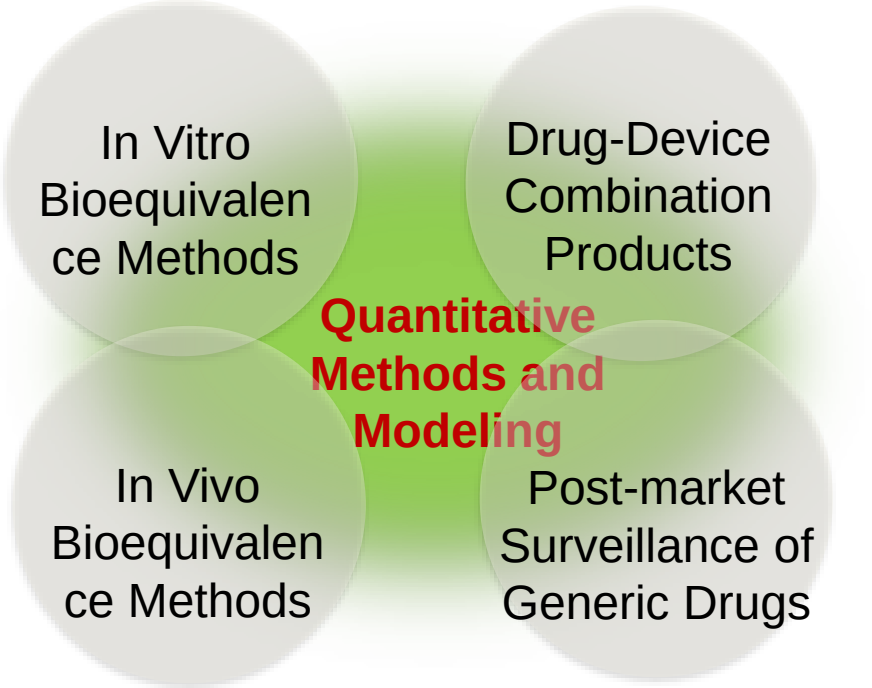
Quantitative Methods & Modeling (QMM) for Generic Drug Development and Approval



Model integrated evidence (MIE) refers to using model generated information such as the virtual bioequivalence (VBE) study results not just to plan a pivotal study but to serve as pivotal evidence

Clin Pharmacol Ther. 2019 Feb;105(2):338-349

QMM/MIE Impact Various Regulatory Activities in the Office of Generic Drugs (CY 2020)

	Type	No.	Examples
Regulatory	**ANDA Review Consults**	15	❖ **Particle size distribution space for BE assessment; dose scale analysis with data censoring; model-based CE BE analysis** ❖ Topical dermatological/orally inhaled/long-acting injectable products
	Pre-ANDA Meetings	52	
	Controlled Correspondences	64	❖ Evaluation of alternative BE approaches to the CE study for locally acting products
	BE Guidance	11+	❖ PSGs: New/revised guidance on modified release products; use of pAUC as an additional BE metrics (e.g., methylphenidate)
Research	**Internal Regulatory Research Projects**	56	❖ Assessment of PD endpoints for BE evaluation ❖ BE evaluation methods (e.g., higher-order crossover design, group/batch effects) ❖ BE study interruption during COVID-19 pandemic
	New Contracts and Grants in GDUFA II since 10/2017	35	❖ Development of model-informed BE for complex generic drugs ❖ Modeling platform development (e.g., long acting injectables, sparse sampling) ❖ Development of PBPK model for locally-acting drug products ❖ Characterizing safety and efficacy of generic drugs, and expanding BCS class 3 waivers

ANDA, abbreviated new drug application; BE, bioequivalence; CE, clinical endpoint; PK, pharmacokinetic; PD, pharmacodynamics; PBPK, physiologically based PK; PSG, product-specific guidance; BCS, Biopharmaceutics Classification System; pAUC, partial area under the curve.

Alternative Analysis Approaches for COVID-19-Interrupted Studies

Background: The COVID-19 pandemic impacted clinical study execution, including those for ANDAs. Study interruptions can arise from:

Exposure risk | Travel limitations | Site closures | Test/Reference availability

Question: If a reference product expires in an ongoing pivotal PK BE study which is interrupted due to the COVID-19 pandemic, and two batches of a reference (R) product have to be used, how would the BE results be evaluated?

Solution: M&S provided scientific justification to use certain alternative analysis approaches for unexpected changes on study execution during the COVID-19 pandemic, such as having two batches of an R product in a single PK BE study.

- M&S showed that alternative analysis approaches may be used to incorporate batch difference for BE establishment when two batches of R were used.
- The acceptability of BE results is based on study type, statistical method, and would be case specific.

E.g.

Interruption

	Period 1	Period 2	Period 3	Period 4
Sequence 1	T	R1	T	R2
Sequence 2	R1	T	R1	T

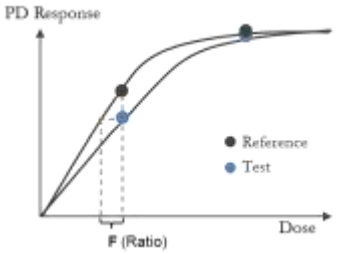
https://www.grxbiosims.org/learning-track/alternative-be-approaches-due-to-covid19-related-study-interruptions/
https://www.fda.gov/drugs/coronavirus-covid-19-drugs/bioequivalence-studies-submission-andas-during-covid-19-pandemic

Likelihood Model Based Data Imputation to Support BE Evaluation for Albuterol Sulfate Inhalation Aerosol

Albuterol Sulfate Inhalation Aerosol: a beta$_2$-adrenergic agonist indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older.

- **Public Health Emergency Designated COVID-19 Generic Drug Product**
- **First Generic Priority ANDA**

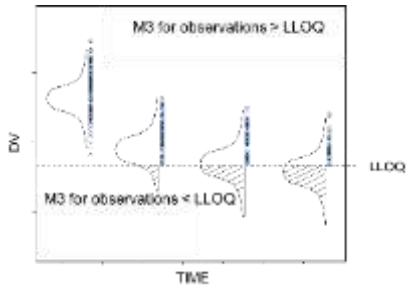
Background: PD BE bronchoprovocation study conducted by the applicant included considerable amount of censored values (out of detection limit) in PC20 data.



Question: How to assess PD BE given the high percentage of censored values in the study data?

Solution: FDA's internal analysis adopted a modern likelihood-based modeling approach (M3 model) to perform data imputation for censored values.

Regulatory Impact: This modeling approach improved the credibility of the PD model and provided model-integrated evidence to support the final ANDA approval as one of the first generics in 2020.



PBPK Absorption Model in Assessing the Impact of Particle Size Distribution (PSD) on BE

A Capsule Product: efficacy related to systemic drug exposure.

Background: PK parameters, e.g., Cmax and AUC are found to be sensitive to changes in mean particle size of the active pharmaceutical ingredient under fasting condition. There is a PSD deviation in terms of D90 between test and reference product.

Question: What is the effect of PSD deviation on bioequivalence?

Solution: PBPK modeling and simulation by the FDA assessor suggested that the test vs reference PK metrics showed a low risk of non-BE when D90 varied over a wide range with a certain fixed value of D50 for all strengths.

Regulatory Impact: The modeling results supported a satisfactory BE assessment of this ANDA and setting a clinically relevant 3 tier PSD specification.

Formulation	D10	D50	D90	Test/Reference Ratios			BE
				Cmax	AUCt	AUCinf	
Refence	X10	X50	X90				
Test 1	X10--	X50	X90--	107	105	106	Pass
Test 2	X10-	X50	X90-	1	98.3	98.2	Pass
Test 3	X10+	X50	X90++	81.2	81.5	81.3	Pass
Test 4	X10+	X50	X90+++	80.3	79.8	80.3	Fail

Simulation results with fixed D50 and changed D10 and D90 using the reference upper bound PSD

Advancing QMM/MIE for Complex Products

- Model informed development of in vitro (only) BE approaches
  - Identification of clinically relevant attributes and the associated BE space
  - Modeling and simulation for in vitro testing results. E.g., Modeling In Vitro Permeation Testing (IVPT) results
- Alternative approach to replace comparative pharmacodynamic/clinical endpoint BE studies as appropriate
  - Correlate PK metrics based on systemic PK exposure to action site exposure and/or clinical response
  - Modeling for regional drug depositions for orally inhaled products (**Breakout-Session 1A**)
- Model integrated evidence for generic drug approvals
  - Platform for virtual BE simulations
  - Sufficiently verified and validated model to generate virtual BE results
  - E.g., Long acting injectables (**Breakout-Session 1B**)

QMM/MIE to Support In Vitro & In Vivo BE Approaches for non-Complex Products

- QMM to support a further abbreviated in vivo program for BE assessment (**Breakout-Session 3A**)
  - BCS 3 Biowaivers for more general cases
  - Not conducting fed BE study in high confidence scenarios
  - Lower strength waiver under special conditions
    - Risk assessment for modified release products
- QMM to modernize the in vivo BE programs with novel study designs
    - BE assessment based on steady state PKs (e.g., long acting injectables + oncology) (**Breakout-Session 1B & 3B**)
  - Bridging BE across different populations
    - Healthy -> pediatric and geriatric
    - Healthy -> patient population

Introducing Artificial Intelligence and Machine Learning to Generic Drug Development and Regulatory Assessment

- In vitro-in vivo connections
  - Formulation effects on dissolution profiles and PK exposure
  - In vitro-in vivo correlations
  - Effect of manufacturing process
- Improving conventional pharmacometrics toolsets
  - Model building and model selection
- Machine learning and natural language processing for knowledge management
  - Knowledge collection for FDA assessors
  - PK data warehouse
  - Review automation
    - Text mining and text generation
  - Tools to enhance review efficiency, consistency, and quality
- For further information, please attend **Breakout-Session 1C**

Industrial Implementation and Use of Quantitative Methods and Modeling

- Sufficient communication between the agency and industry in terms of expectation in the modeling package is key to successful implementation

- Awareness of value creation by using modeling and simulation toolsets to support regulatory decision making is an important start

Seeking Your Input on Future Research under the GDUFA Regulatory Science Program!

- Alternative metrics to replace comparative pharmacodynamic/clinical endpoint BE studies as appropriate
- Biowaivers (BCS, lower strength under special conditions)
- Food effect BE study
- Model supported in vitro characterizations
  - BE space for testing parameters
- Novel BE study designs