Leveraging Quantitative Methods in Reviewing Complex/Locally Acting Products

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October 2, 2017

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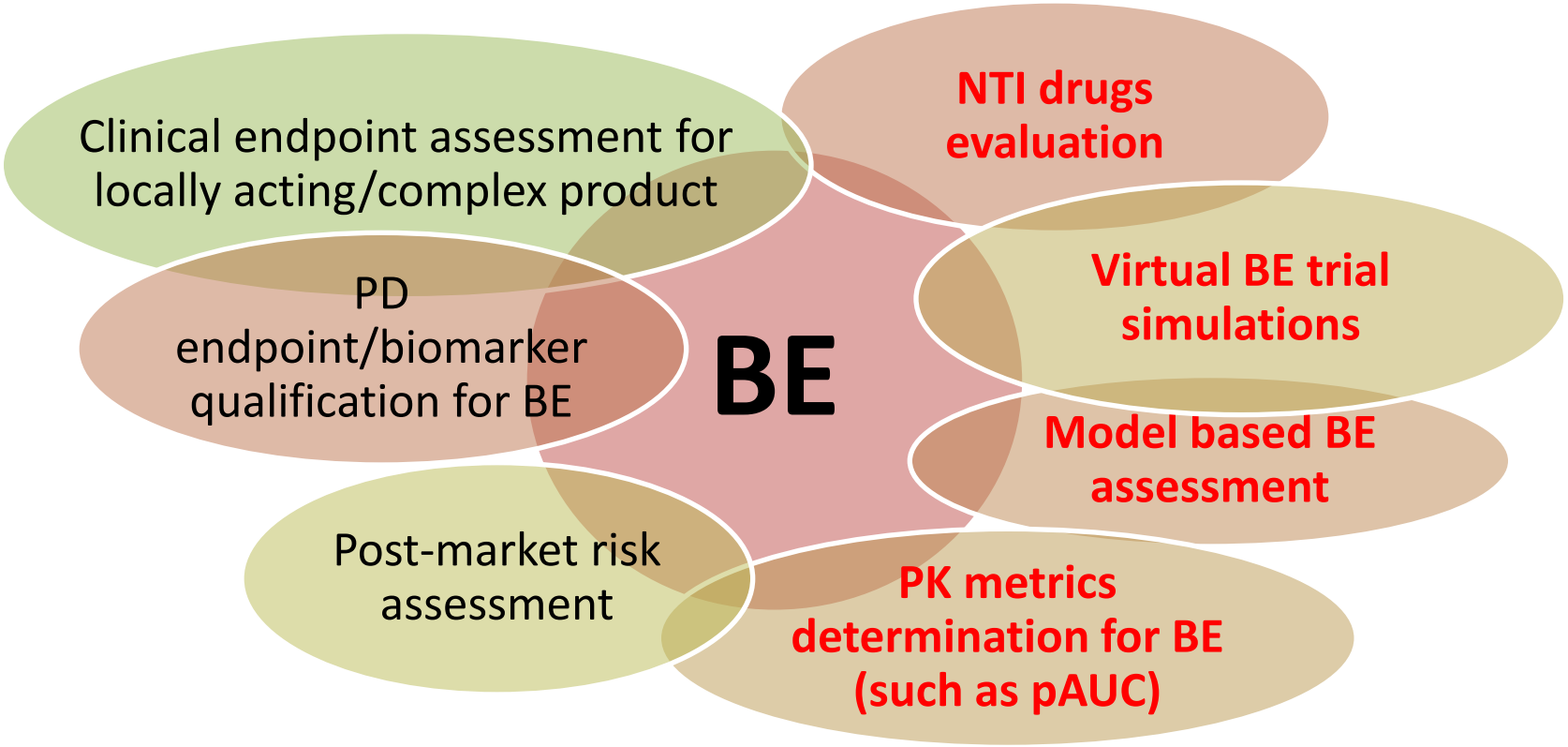
- I do not have any financial interest or conflict of interest with any pharmaceutical companies.

Quantitative Clin Pharm (QCP)

- Widely used in new drug development, but not usually a part of generic drug development
  - Population PK analysis, PK-PD modeling, Exposure-Response (E-R) analysis, and clinical trial simulation
- FDA is shifting from one-size-fits-all paradigm to risk-based product-specific regulatory system
  - Risk-based BE recommendations for NTI drugs
  - pAUCs for some modified release products
- Bioequivalence (BE) trial simulations can inform generic drug development and review
- Efficient tools to prioritize surveillance efforts of generic substitution signals
  - Methylphenidate, Warfarin, etc.

General QCP Model Applications for Generic Products



NTI: narrow therapeutic index; pAUC: partial area under concentration-time curve; PD: pharmacodynamics

Courtesy slide from Dr. Liang Zhao

Product Specific Guidance (PSG) for NOACs

Novel Oral Anti-Coagulants

- Dabigatran (PRADAXA)- thrombin inhibitor
  - Approved October 2010
  - Draft PSG posted (2012)
  - Revised draft PSG posted (2015)
- Rivaroxaban (XARELTO)-factor Xa inhibitor
  - Approved November 2011
  - Draft PSG posted (2015)
- Apixaban (ELIQUIS)-factor Xa inhibitor
  - Approved December 2012
  - Draft PSG posted (2013)
  - Revised draft PSG posted (2017)
- Edoxaban (SAVAYSA)-factor Xa inhibitor
  - Approved January 2015
  - Draft PSG posted (2017)
- Betrixaban (BEVYXXA)-factor Xa inhibitor
  - Approved June 2017
  - Draft PSG pending

PSGs are listed at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075214.htm

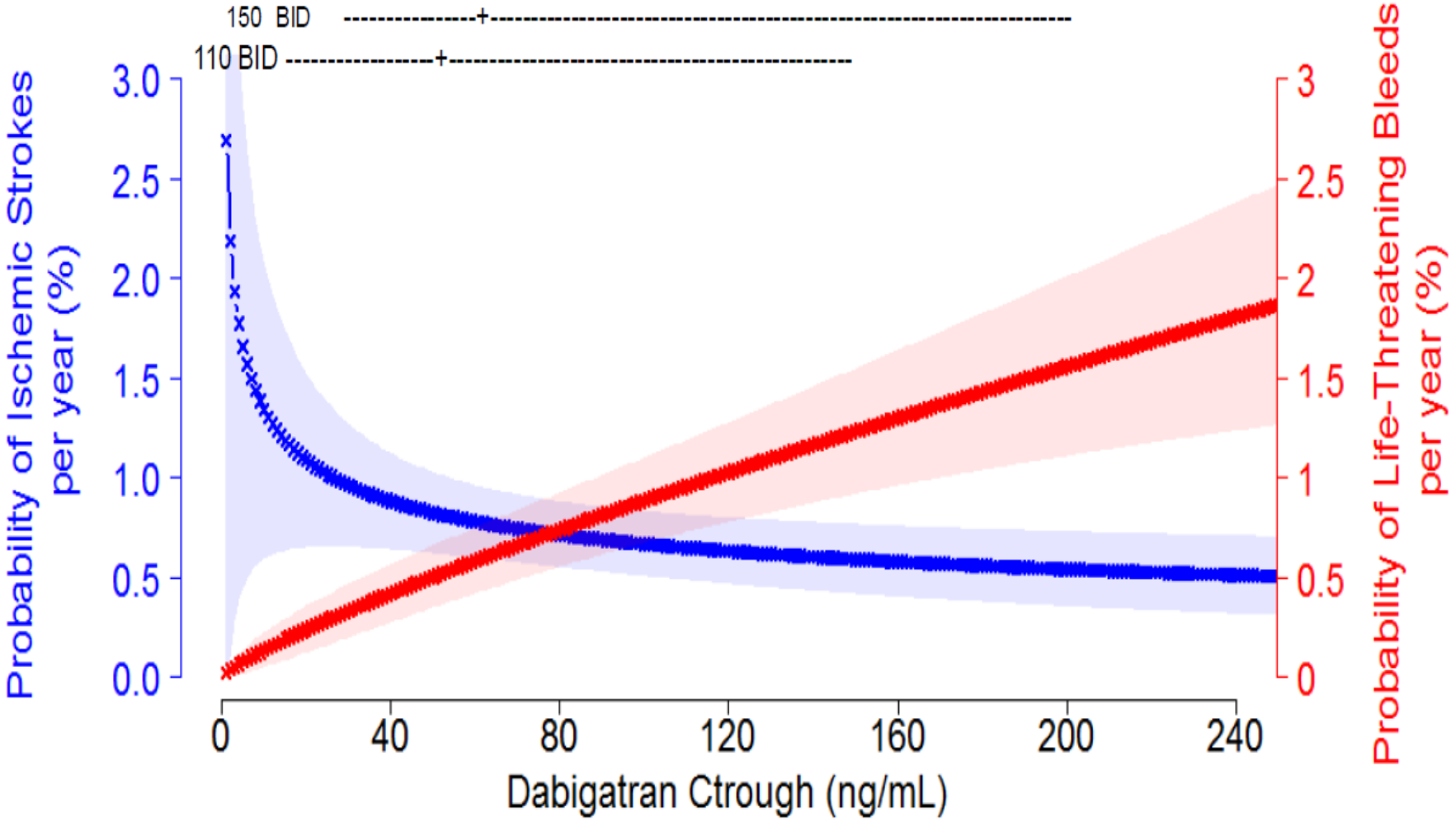
Dabigatran 2012 PSG: Focusing on high PK Within-Subject Variability (WSV)

Draft PSG in 2012 stated that

"Applicants may consider using a reference-scaled average bioequivalence approach for dabigatran etexilate. Please refer to Progesterone Capsules Guidance for information regarding statistical analysis method using the reference scaled average bioequivalence approach."

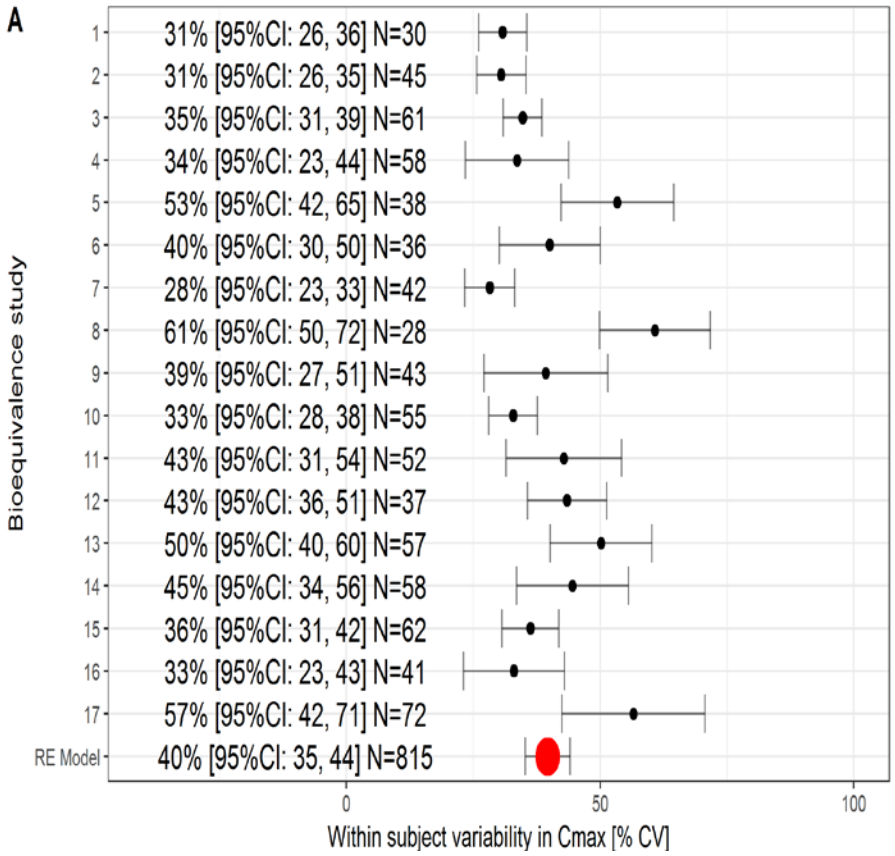
A wider BE limit is implied!

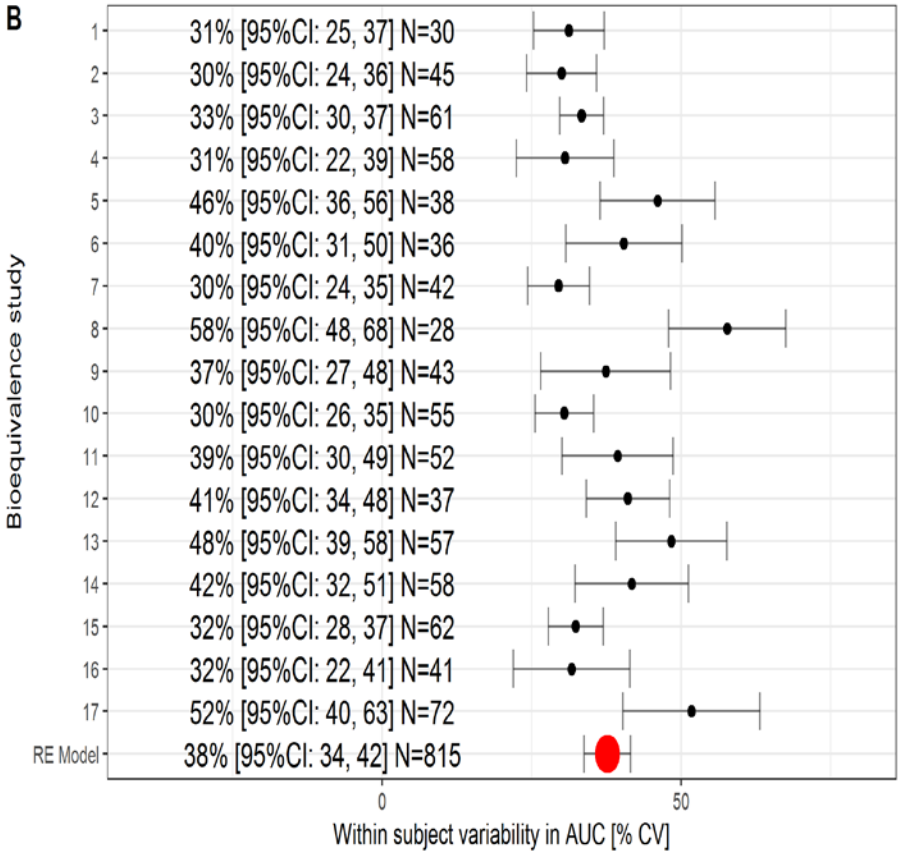
Steep E-R for Efficacy and Safety



https://wayback.archive-it.org/7993/20170405211258/https:/www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM421612.pdf

Dabigatran PK WSV: Meta-analysis with Replicated BE Studies





- Dabigatran has high PK WSV
- WSV is highly variable across different studies

Dabigatran PSG Revision in 2015

Additional comments: Dabigatran demonstrated a steep exposure-response relationship for both efficacy and safety.[1] Therefore, applicants should not use the reference-scaled average bioequivalence approach to widen the BE limits for dabigatran bioequivalence evaluation. Applicants should use the average bioequivalence approach with BE limits of 80-125%. The within-subject variability of test and reference products should be compared and the upper limit of the 90% confidence interval for the test-to-reference ratio of the within-subject variability should be $\leqslant 2.5$. For details about the Method for Statistical Analysis comparing within-subject variability of test and reference products, refer to *Guidance on Warfarin Sodium*.

- Revision taking into account that dabigatran has demonstrated a steep exposure-response relationship for safety/safety and large WSV;
- Revision is presented as a positive, proactive, science-based course of action;
- Important to support postmarket surveillance in light of emerging reports of safety concerns with dabigatran.

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM544879.pdf

Use of QCP in Complex Drug Products BE Assessments

- Complex products are complex in their own ways that pose challenges in generic drug development.
- Office of Generic Drugs spends an increasing amount of time conducting research, and developing standards and policy for complex drug products, to ensure the development and approval of future generic products that demonstrate equivalence to increasingly complex RLDs.
- QCP approaches are essential
  - Help to make decisions consistently in a quantitative way
  - Serve as the support for efficient innovative BE approaches
  - Integrate different BE approaches (in vitro studies, PK studies, PD studies) and set clinically relevant BE criteria

QCP For Faster and Better Decisions

Case Study with topical products

- The case study presented here are examples of using model-based BE approach in the framework of equivalence testing in Rosacea patients.
- The classical equivalence testing includes hypothesis testing based on differences in treatment success rates only at pre-specified time points of interest, although clinical endpoints are frequently measured.
- The model-based approach uses all data collected in the BE studies and even prior knowledge from NDA phases to derive an estimate

Convention on Establishing BE

for Topical Products Indicated for Rosacea

- Clinical endpoint BE studies
  - Measure clinical response (efficacy) in patients
  - Test/RLD/Placebo
  - Both Test and RLD must be superior to Placebo
  - Test must be BE to RLD

Active Ingredient	Formulation	Clinical Endpoint BE
Azelaic Acid	Topical Gel/Cream	√
Metronidazole	Topical Gel/Cream/Lotion	√
Brimonidine	Topical Gel	√

Brimonidine Topical Gel

RLD	MIRVASO topical gel (NDA 204708)
Approved Indication(s)	Topical treatment of persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older
Mechanism of Action	• A relatively selective alpha-2 adrenergic agonist. • Reduce erythema through direct vasoconstriction.
Absorption	Minimal systemic absorption
Primary Efficacy Endpoint in NDA	Composite success: proportion of subjects with a 2-grade improvement on both 5-point CEA and PSA measured at hours 3, 6, 9, and 12 on Day 29
Draft PSG on BE demonstration	Posted on 9/2015 Primary: Hours 3, 6, 9, and 12 on Day 15 Secondary: Hours 3, 6, 9, and 12 on Day 1

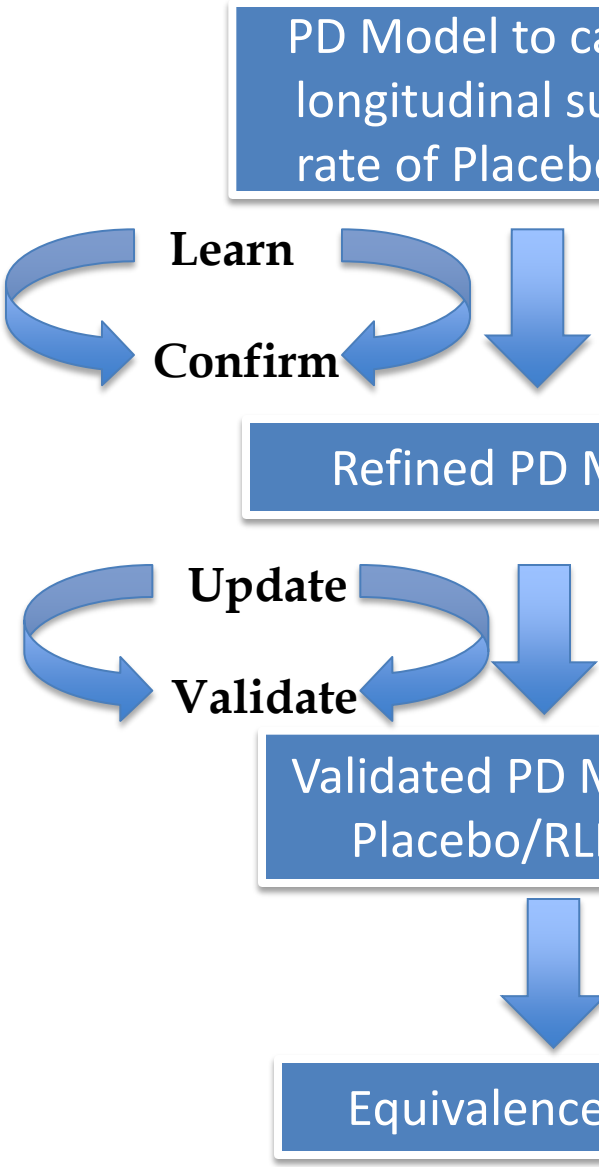
CEA: Clinical Erythema Assessment; PSA: Patient Self Assessment
PSG available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075214.htm

ANDA1 Study Design is Incomplete

- The clinical endpoint BE study was conducted prior to the PSG post and didn't include clinical efficacy assessment on all recommended time points.
- Primary endpoint was composite success rate at Hour 6 on Day 15;
- Secondary endpoints included assessment on additional time points on Days 1 and 15, but incomplete as compared to the PSG

Question: how about unstudied time points? Approvable or not?

Proposed Workflow



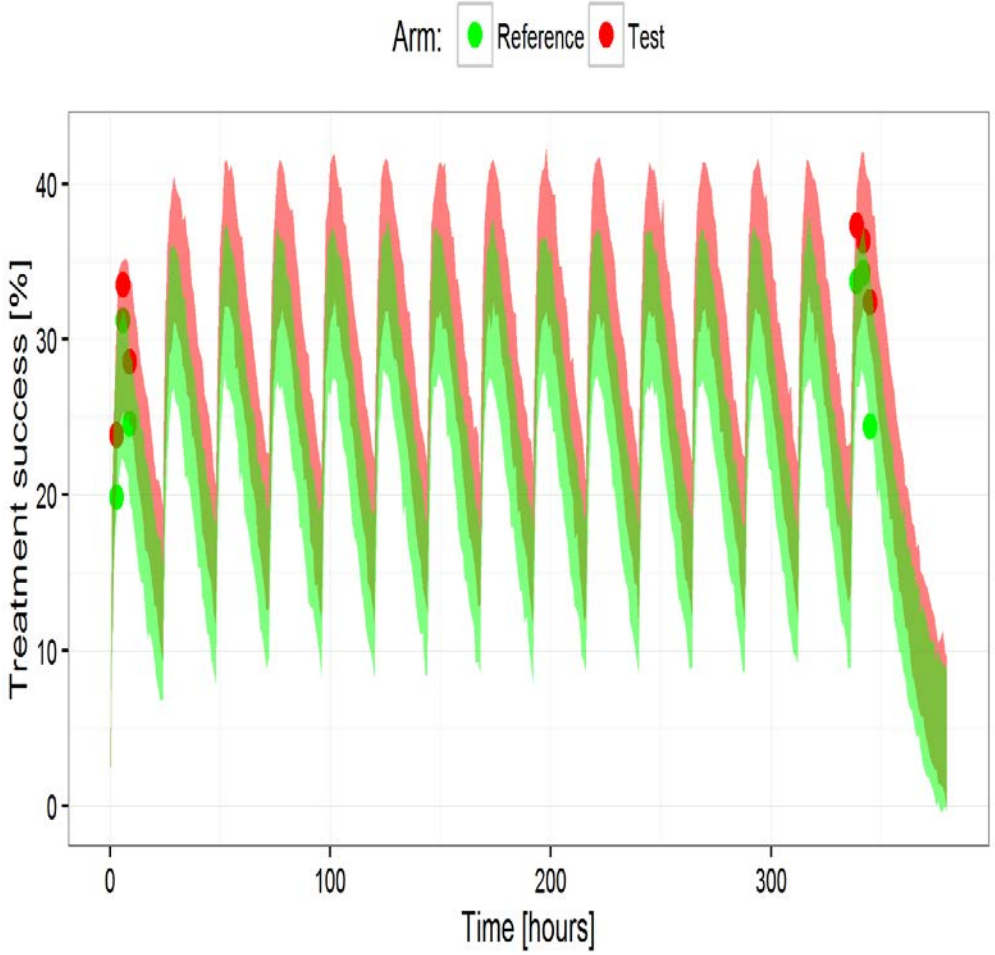
NDA data and literatures

Data from RLD and placebo treatment in ANDA1

Data from Test treatment in ANDA1

Clinical endpoint BE trial simulations

PD Model can Adequately Describe Observed Efficacy in ANDA1



- ANDA1 study design:
  - RLD=183; Test=184; Placebo=185
  - Daily dosing for 15 days
  - Treatment success rate recorded at Days 1 and 15 (placebo corrected, Green/Red Points)
- Simulations w/ PD model
  - Same design as above
  - The shaded green and red areas represent the 90% prediction interval of simulated placebo-corrected treatment success rate for RLD and test products, respectively.

Trial Simulations Predict that Test Product is Equivalent

Time (Day 15)	Test (N=168)	RLD (N=170)	90% Confidence Interval	Result
Hour 3	36.31	34.12	[-0.0694, 0.1133]	Pass
Hour 6	35.71	34.12	[-0.0752, 0.1072]	Pass
Hour 9	31.55	24.71	[-0.0177, 0.1546]	Pass
Hour 12	30.95	25.88	[-0.0263, 0.1345]	Pass

- The predicted placebo-corrected success rates are presented for Test and RLD, respectively.
- The estimated 90% confidence interval for the difference of the success rates between test and RLD products is contained within the interval [- 0.20, 0.20].
- Similar simulation results on Day 1.
- **This simulation work conducted by FDA supported the tentative approval decision of the application.**

Moving Forward

- Actions moving forward
  - FDA: Post PSG early and timely
  - Applicant: meet with FDA if PSG of a complex product is not posted
- Under GDUFAII
  - FDA has Pre-ANDA program to clarify regulatory expectations early in product development
  - For complex products, applicant can have product development meetings, pre-submission meetings and mid-review cycle meetings
  - Non-complex NME drugs, PSG at least 2 years prior to lawful ANDA filing
  - PSG for complex drugs will be issued as scientific recommendations are available

Quantitative Methods and Modeling in Regulatory Submissions

- Can serve as a support for alternative efficient BE approaches in the Pre-ANDA meeting discussions
- FDA will review the modeling and simulation reports in the meeting packages and all regulatory submissions!
- Help to assess the BE approach
  - Is it a sensitive BE approach to detect product differences?
  - How big is the effect size?
  - Is the population appropriate (inclusion/exclusion criteria)?
  - Is the dose level appropriate (dose-response curve)?
  - Sample size? Study duration? When to assess BE?

Conclusions

- **The model-based BE approaches are essential for complex products**, if ANDA applicants want to conduct BE studies in an efficient way
  - Quantitatively evaluate the study design and sensitivity
  - Maximize the information gained from efficient BE studies
    - Save subjects/time/cost and eventually reduce drug cost!
  - Critical in ANDA reviews, PSG development, and almost all regulatory activities
- Future work
  - Engage all stakeholders (FDA + industry)
  - Technical improvement

GDUFA Regulatory Science Program

- Model based BE
  - Evaluation of model-based bioequivalence statistical approaches for sparse design PK studies (University of Paris);
  - Evaluation and development of model-based bioequivalence analysis strategies (Uppsala University);
- Long-acting injectable products
  - Pharmacometric modeling and simulation for evaluation of bioequivalence for leuprolide acetate injection (University of Utah);
  - Data-fusion based platform development of population PKPD modeling and statistical analysis for bioequivalence assessment of long-acting injectable products (University of Massachusetts);
- NTI products
  - Population pharmacokinetic and pharmacodynamic, dose-toxicity modeling and simulation for narrow therapeutic index (NTI) drugs (University of Maryland);
- Post-market generic swithability risk
  - Pharmacometic modeling and simulation for generic drug substitutability evaluation and post marketing risk assessment (University of Maryland);
  - A model and system based approach to efficacy and safety questions related to generic substitution (University of Florida);
- pAUC assessment
  - Pharmacometric modeling of immunosuppressants for evaluation of bioquivalence criteria (University of Utah);

Acknowledgement

ORS

- Zhichuan (Matt) Li
- Mario Gonzalez Sales
- Jianghong Fan
- Hyewon Kim
- Satish Sharan
- Stephanie Choi
- MJ Kim
- Liang Zhao
- Lei Zhang
- Robert Lionberger

OB

- Ying Fan
- Zhuo J Zhang
- Carol Kim
- Andrew Fine
- Daiva Shetty
- Mark Ritter
- Sarah Yim
- Ethan Stier
- Bing Li
- Nilufer Tampal

OCP

- Jeffery Florian
- Rajnikanth Madabushi
- Yaning Wang

Backup slides