Marriage Between Quantitative Approaches and Regulatory Science: a Reality Check on Where We Are

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Disclaimer

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

GDUFA Regulatory Science Program

- Supports access to high quality generic drugs in all product categories
  - inhalation, nasal, topical dermatological, ophthalmic, liposomal, sustained release parenteral, solid oral products
- Development of new tools to evaluate drug equivalence and support drug development
  - Model-based bioequivalence (BE) assessment
  - Simulation tools to predict drug absorption
  - Advanced analytical methods for product characterization
  - In vitro methods to predict in vivo performance

GDUFA: Generic Drug User Fee Amendments, 2012
More information available at: www.fda.gov/GDUFARegScience

GDUFA Regulatory Science Priorities (FY17)

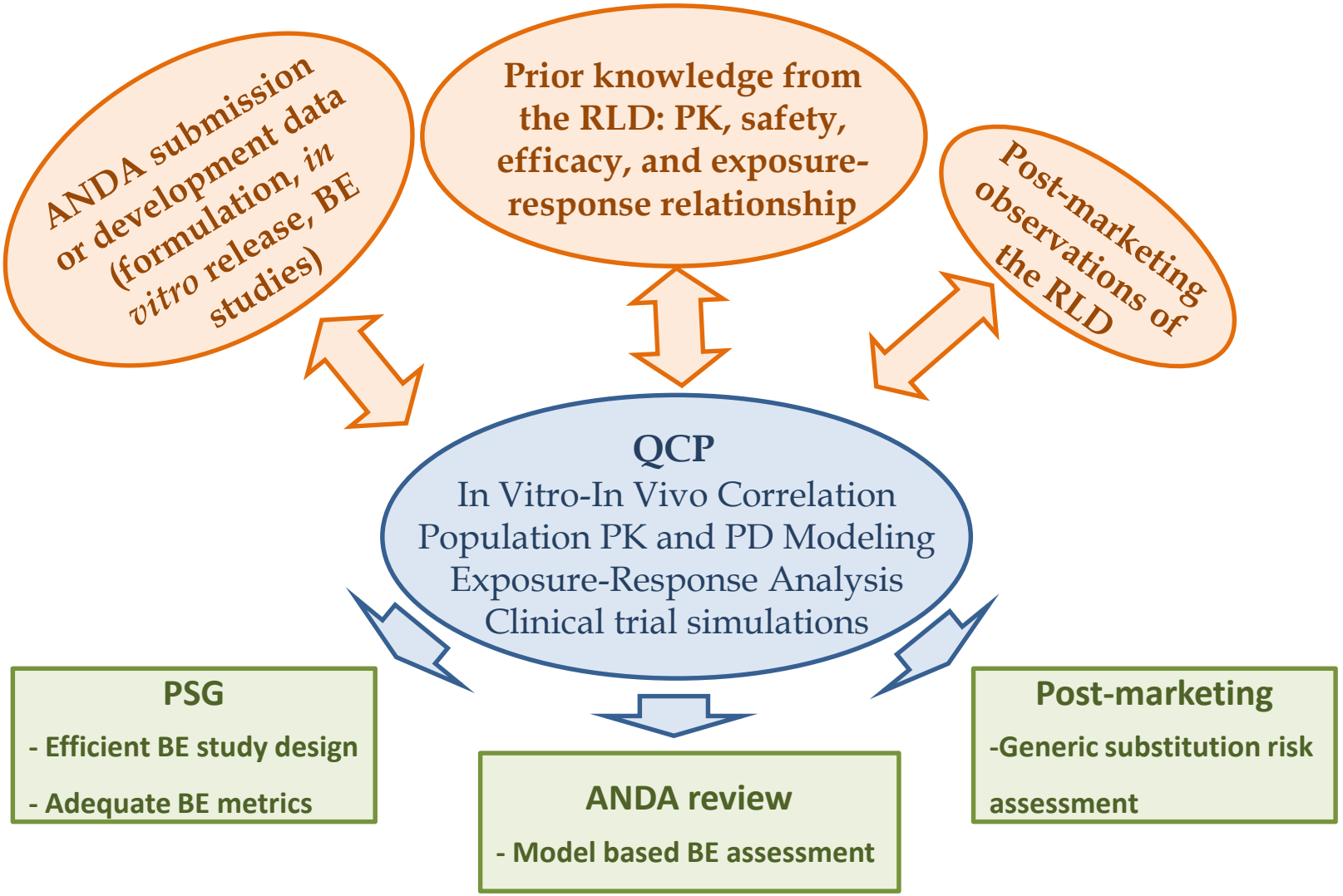
- Topic 1: Post-market evaluation of generic drugs
- Topic 2: Equivalence of complex drug products
- Topic 3: Equivalence of locally acting products
- Topic 4: Therapeutic equivalence evaluation and standards
- Topic 5: **Computational and analytical tools**

https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM526900.pdf

Past and Current State

- Prior to GDUFA I: limited applications of modeling and simulation approaches in generic drug submissions and regulatory reviews
- During GDUFA I: quantitative clinical pharmacology (**QCP**) tools are used to accelerate the development of guidance and improve the consistency of the recommendations
  - Risk-based BE recommendations for narrow therapeutic index (NTI) drugs
  - pAUCs for some modified release products

QCP: Modernize Generic Development

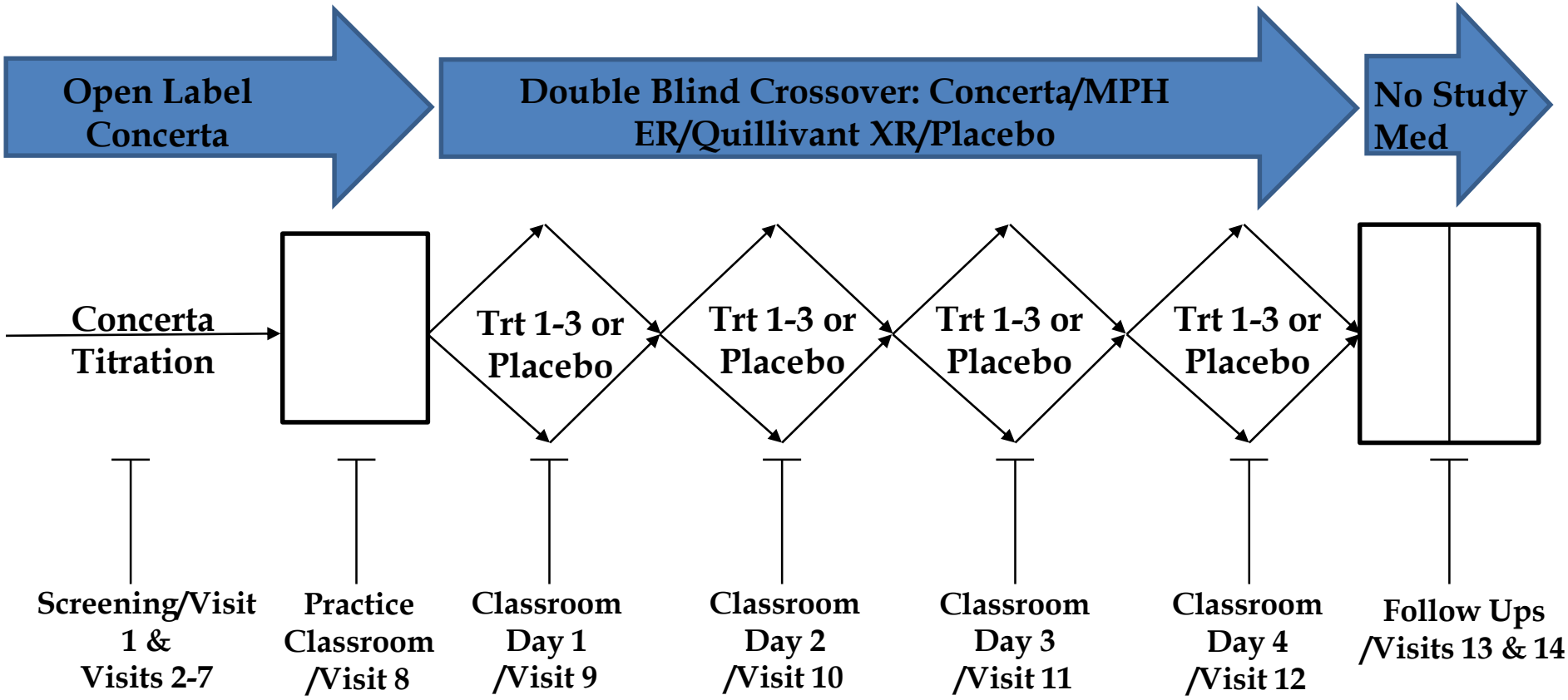


QCP: quantitative clinical pharmacology; ANDA: abbreviated new drug application; RLD: reference listed drug; PSG: product specific guidance

GDUFA Regulatory Science Program

- One hundred and nine (**109**) extramural grants/contracts awarded since 2013 by the **Office of Research and Standards** in the Office of Generic Drugs
  - External collaborations: academia, industry
  - Internal collaborations: FDA labs, other government agencies
- Some QCP team initiated grants/contracts are presented in the following slides

PK/PD Study of MPH ER products in Pediatric ADHD Patients



- Awarded to the Massachusetts General Hospital in September 2014; still ongoing
- To **simultaneously** collecting individual PK (via **dry blood spot sampling)** and PD data in pediatric ADHD patients (6-12 years of age)
- MPH ER: methylphenidate extended release
- ADHD: attention deficit hyperactivity disorder

NTI Drugs

- **Clinical practice data to aid NTI drug classification**
  - Awarded to the Duke University (1U01FD004858) in September 2013 and completed in 9/30/2016.
  - Collected drug dose adjustment and therapeutic monitoring data in patients
- **Therapeutic index evaluation for tacrolimus, sirolimus and levetiracetam**
  - Awarded to the Johns Hopkins University (1U01FD004859) in September 2013 and completed 3/31/2015.
  - Collected population drug monitoring data and clinical PD data from 3 separate institutions.
- **Population PK/PD dose-toxicity modeling and simulation for NTI drugs**
  - Awarded to the University of Maryland, Baltimore (1U01FD0005188) in September 2014. The project is still ongoing.
  - Using principles of PK, PD, and steepness of the PK/PD relationship to propose quantitative metrics for identifying NTI drugs and propose BE criteria for generic NTI drugs.

Pharmacometric and Statistical Analysis: Long Acting Injectable (LAI) Products

- Awarded to the University of Utah (1U01FD005442) and the University of Massachusetts, Lowell (1U01FD005444) in September 2015. These projects are still ongoing.
- To conduct PK/PD modeling and statistical analysis for LAI products to identify appropriate PK metrics and ways to reduce residual PK variability. This allows for BE assessment in parallel BE studies with reasonable sample size.

Model-Based BE Assessment

- Evaluation of Model-Based Bioequivalence (MBBE) Statistical Approaches for PK Studies with Sparse Design
  - Awarded to University Paris, France (HHSF223201610110C) in September 2016. The project is still ongoing.
  - To develop and evaluate new model-based approaches for assessment of BE in sparse PK designs.
- Evaluation and Development of MBBE Analysis Strategies
  - Awarded to Uppsala University (HHSF223201710015C) in April 2017. The project is still ongoing.
  - To develop new population MBBE analysis strategies applicable in both rich and sparse PK study design settings and independent of model structure. (Details to be presented by **Dr. Andrew Hooker.**)

Post-market Generic Substitution

- Awarded to the University of Maryland, Baltimore (1U01 FD0005192) and the University of Florida (1U01FD0005210) in September 2014. These projects are still ongoing.
- UM project uses advanced pharmacometric analysis to devise a novel signal-to-noise ratio classification system that rank orders therapeutic areas to further probe post-marketing reports.
- UF project investigates a risk-based systems pharmacology approach to address issues of post-marketing risk of generic drugs and to interpret post-marketing adverse event reports or complaints related to product substitution. (Details to be presented by **Dr. Larry Lesko.**)

Impact of GDUFA Regulatory Science

- Advance the science of equivalence
  - Prioritize tools and science that make equivalence evaluation consistently in a quantitative way
- Research leads to high quality generic products in all product categories
  - Standards and post-approval monitoring build confidence in generic drug substitution

Regulatory Science – FY17 Impact

- Regulatory Impact
  - Development of product-specific guidances (PSGs):
    - 108 new guidances
    - 86 revised guidances
  - Facilitate Pre-ANDA meeting discussions
  - Resolve complex review issues in ANDA & other submissions
    - Case example on topical products
- Communications:
  - Public workshop: **Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review; October 2 - 3, 2017**
  - Publications: 23
  - External Presentations: 62
  - External Posters: 88

Model-Based Equivalence assessment

A Case Study with Topical Products

- The case study presented here is an example 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

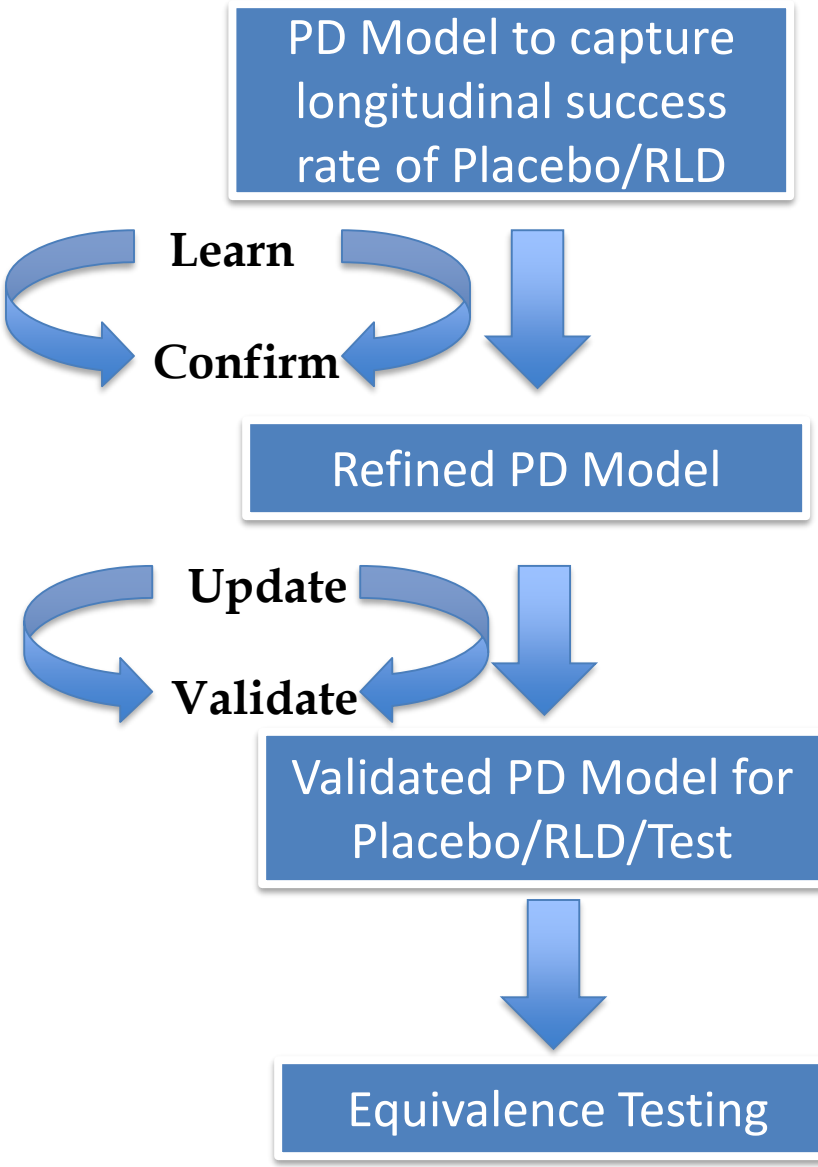
CEA: Clinical Erythema Assessment; PSA: Patient Self Assessment; PSG available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075214.htm

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



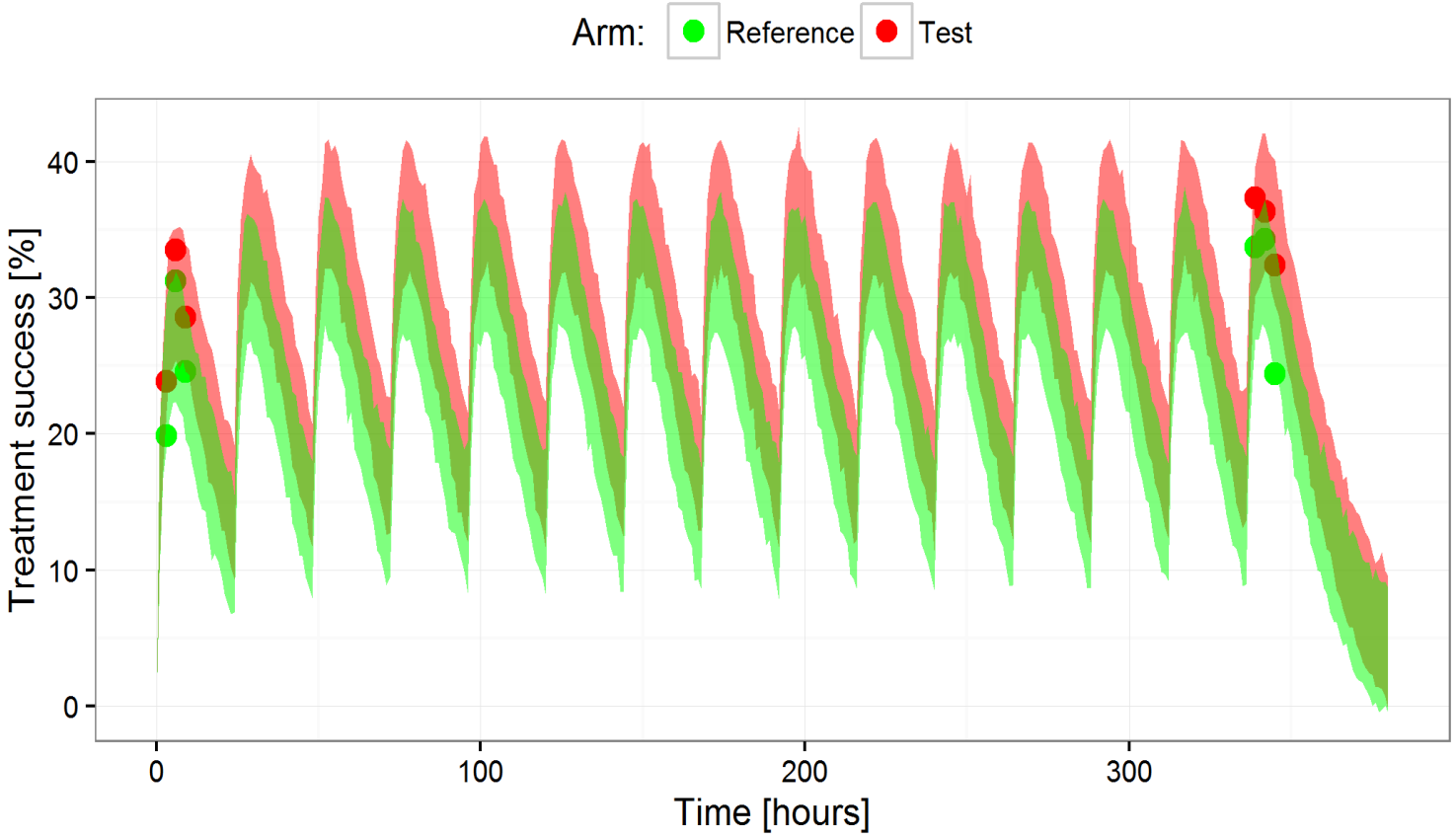
NDA data and literatures

Data from RLD and placebo treatment in ANDA1

Data from Test treatment in ANDA1

Clinical endpoint BE trial simulations

PD Model Adequately Describes Observed Efficacy in ANDA1



- In ANDA1: daily dosing for 15 days; the sample size for RLD, Test and placebo arms are 183, 184, and 185, respectively.
- Green/Red Points: placebo corrected treatment success rates recorded at Days 1 and 15
- Shaded green and red areas: 90% prediction interval of simulated placebo-corrected treatment success rates for RLD and test products

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
- 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 the FDA supported the approval decision of the application.**

Conclusions on the Case Study

- **The QCP tools are essential for new BE approaches of 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)
    - FDA: Pre-ANDA program to clarify regulatory expectations early in product development
    - Applicant: meet with FDA if PSG of a complex product is not posted
  - Technical improvement (FDA + industry + academia)

Take Home Messages

- Regulatory science enhancements under GDUFA allow a greater interaction with industry and the public for feedback on research initiatives
  - FDA is engaging with leading M&S experts from across the world to ensure that the regulatory review of generic drugs is based on the best available science
- Outcomes from GDUFA research studies have contributed to development of guidances and recommendations to industry
- There is an increasing need to develop alternative efficient bioequivalence methods for complex products
  - More collaborations are needed!

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