Non-traditional Approaches to Bioequivalence AND Application of Clinical Pharmacology to Minimize Barriers to Generic Drug Substitution

November 6, 2018

Kathleen Uhl, MD

Director, Office of Generic Drugs

CDER, FDA

Learning Objectives

Learning Objectives:

- Upon completion, participants will be able to describe the FDA's role in generic review and approval, specifically related to bioequivalence.
- Upon completion, participants will be able to describe limitations to the use of clinical endpoint studies in generic drug development and regulatory review.
- Upon completion, participants will be able to describe newer approaches to demonstrate bioequivalence of generic drug products.

Session Description

- Provides an overview of the generic drug approval process, with select emphasis on bioequivalence determination.
- Review traditional approaches to bioequivalence for generic drug applications, e.g., PK/PD.
- Discuss use of clinical endpoint studies and its limitations.
- Discuss approaches to characterize critical performance elements of complex generic drug products for more efficient generic drug development and regulatory decision making.
- Consider clinical pharmacology tools of quantitative methods and modeling simulation as ways to integrate and bridge existing knowledge to streamline product development and regulatory decisions.

Biography and Contact Information

- Director of Office of Generic Drugs (OGD) at FDA/CDER
- 20 years at FDA in numerous positions
- Undergraduate degree – Temple University
- MD – Medical College of Pennsylvania (now Drexel University)
- Clinical Pharmacology fellowship training at Uniformed Services University
- Adjunct Professor at the Uniformed Services University
- kathleen.uhl@fda.hhs.gov
- https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm119100.htm

OUTLINE

- Generic Drugs and OGD 101
- Bioequivalence
  - Traditional approaches
- Newer approaches

OUTLINE

- **Generic Drugs and OGD 101**
- Bioequivalence
  - Traditional approaches
- Newer approaches

FOUNDATIONS OF GENERIC DRUG APPROVAL

- Approval of generic drug starts with a "listed drug" –
  - Generally, "innovator" drug or "brand-name drug" approved under 505(c)
  - ANDA **relies on** FDA's finding of safety and effectiveness for listed drug
  - **"RLD" OR "reference listed drug"**
- Requires demonstration of **"sameness"**
  - Plus additional information to permit reliance on RLD

NDA vs. ANDA Review Process

NDA Requirements	ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Microbiology	4. Microbiology
5. Inspection	5. Inspection
6. Labeling	6. Labeling
7. Animal Studies	
8. Clinical Studies	7. Bioequivalence
9. Bioavailablity/BE	

Contents of an ANDA: 505(j)(2)

- Identify Single Listed Drug = Reference Listed Drug (RLD)
- Identify Approved Conditions of Use
- Evidence Supporting:
  - Same Active Ingredient
  - Same Route of Administration
  - Same Dosage Form
  - Same Strength
  - Bioequivalence
  - Safety of Inactive Ingredients

Contents of an ANDA (cont'd)

- Chemistry, Manufacturing, and Controls (CMC) Information
  - Components and composition
  - Batch formulation and records
  - Description of facilities
  - Specifications and tests
  - Packaging
  - Stability
- Side-by-Side Comparison of Approved and Proposed Labeling
- Patent Certifications, Exclusivity Information

Contents of an ANDA: 505(j)(2)

- Identify Single Listed Drug = Reference Listed Drug (RLD)
- Identify Approved Conditions of Use
- Evidence Supporting:
  - **Same Active Ingredient**
  - **Same Route of Administration**
  - **Same Dosage Form**
  - **Same Strength**
  - Bioequivalence
  - Safety of Inactive Ingredients

Pharmaceutical Equivalence (PE)

Contents of an ANDA: 505(j)(2)

- Identify Single Listed Drug = Reference Listed Drug (RLD)
- Identify Approved Conditions of Use
- Evidence Supporting:
  - Same Active Ingredient
  - Same Route of Administration
  - Same Dosage Form
  - Same Strength
  - **Bioequivalence**
  - Safety of Inactive Ingredients

ALLOWABLE DIFFERENCES IN GENERICS

- Generics **may vary** in the following:
  - Shape, size, color
  - Scoring configuration
  - Release mechanism
  - Packaging
  - Excipients
  - Buffers, Preservatives, Thickening Agents, Tonicity Adjusters (for Ophthalmic Products)
  - Expiration dating
  - Minor labeling differences
  - Storage requirements
- Generic product cannot have *"significant differences"*, i.e., differences that would impact the safety or efficacy profile

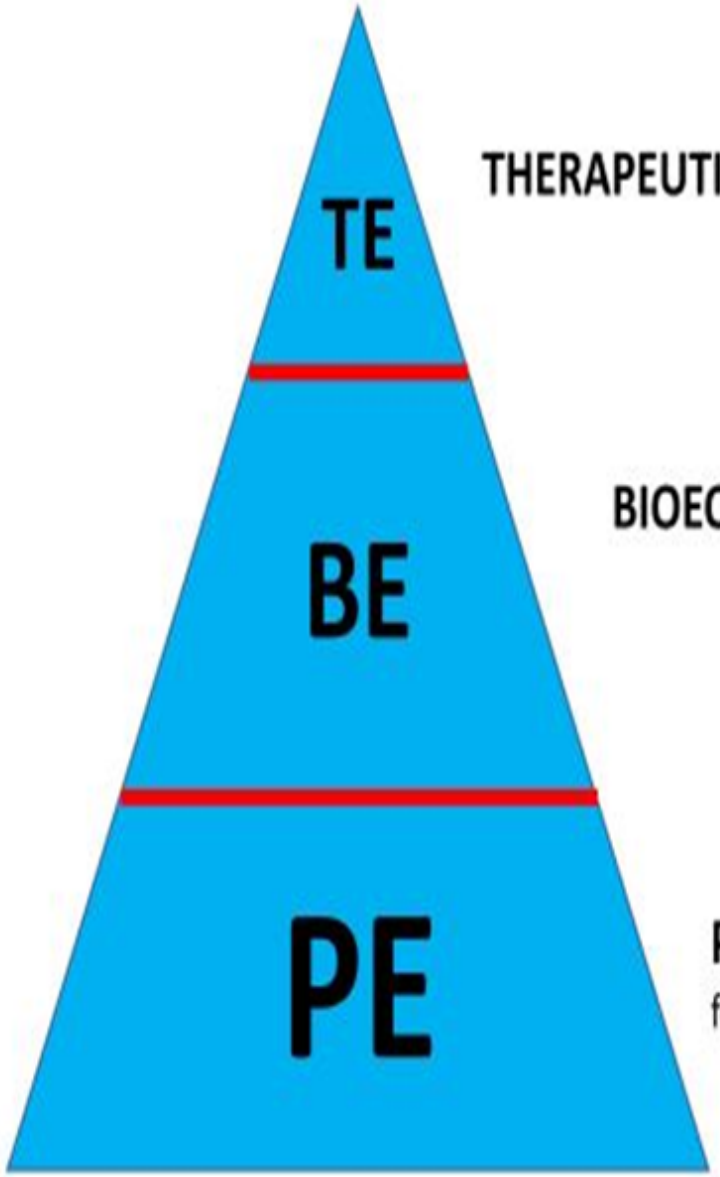
ALLOWABLE DIFFERENCES IN GENERICS

- Generics **may vary** in the following:
  - **Shape, size, color**
  - Scoring configuration
  - **Release mechanism**
  - Packaging
  - **Excipients**
  - **Buffers, Preservatives, Thickening Agents, Tonicity Adjusters** (for Ophthalmic Products)
  - Expiration dating
  - Minor labeling differences
  - Storage requirements
- Generic product cannot have *"significant differences"*, i.e., differences that would impact the safety or efficacy profile

GENERIC SUBSTITUTABILITY

In relation to the RLD, generic drug products are expected to be:

- **Pharmaceutical Equivalence (PE)**
  - Same active ingredient(s) and
  - Same dosage form and
  - Same route of administration and
  - Same strength
- **Bioequivalence (BE)**
  - No significant differences in rate and extent of absorption at site of action
- **Therapeutic Equivalence (TE)**
  - PE + BE
  - Expected to have the **same clinical effect and safety profile** when administered to patients under the conditions specified in the labeling
  - Substitution at the pharmacy level permissible



THERAPEUTIC EQUIVALENCE – same clinical efficacy and safety

BIOEQUIVALENCE – same rate and extent of exposure

PHARMACEUTICAL EQUIVALENCE – the foundational basis for all subsequent equivalency testing

OUTLINE

- Generic Drugs and OGD 101
- **Bioequivalence**
  - **Traditional approaches**
- Newer approaches

BIOEQUIVALENCE (BE)

"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 administrated at the same molar dose under similar conditions in an appropriately designed study…"

(21 CFR §320.1)

BIOEQUIVALENCE STUDIES

Addressing the **primary reason** for BE studies for generics:

- Understanding the **release** of the **drug substance** from the **drug product** into the systemic circulation

DEMONSTRATE BE

BE may be demonstrated with in vivo or in vitro data, or both

1. **Waiver**
   - For drugs that are qualitatively (Q1) and quantitatively (Q2) equivalent
   - Q1 – same components
   - Q2 – same amounts of the same components
2. **PK equivalence**
   - Measure active ingredient or moiety in blood, plasma, etc.
3. **PD equivalence**
   - Where PK is not possible or not related to the therapeutic effect
4. **Comparative Clinical Endpoint BE study**
5. **In Vitro Studies**
   - Dissolution and formulation data, others
6. **Weight of Evidence/Totality of Evidence Approach**
   - Frequently used approach for complex generic drug products, and others
   - Uses multiple orthogonal methods

TO DEMONSTRATE BE

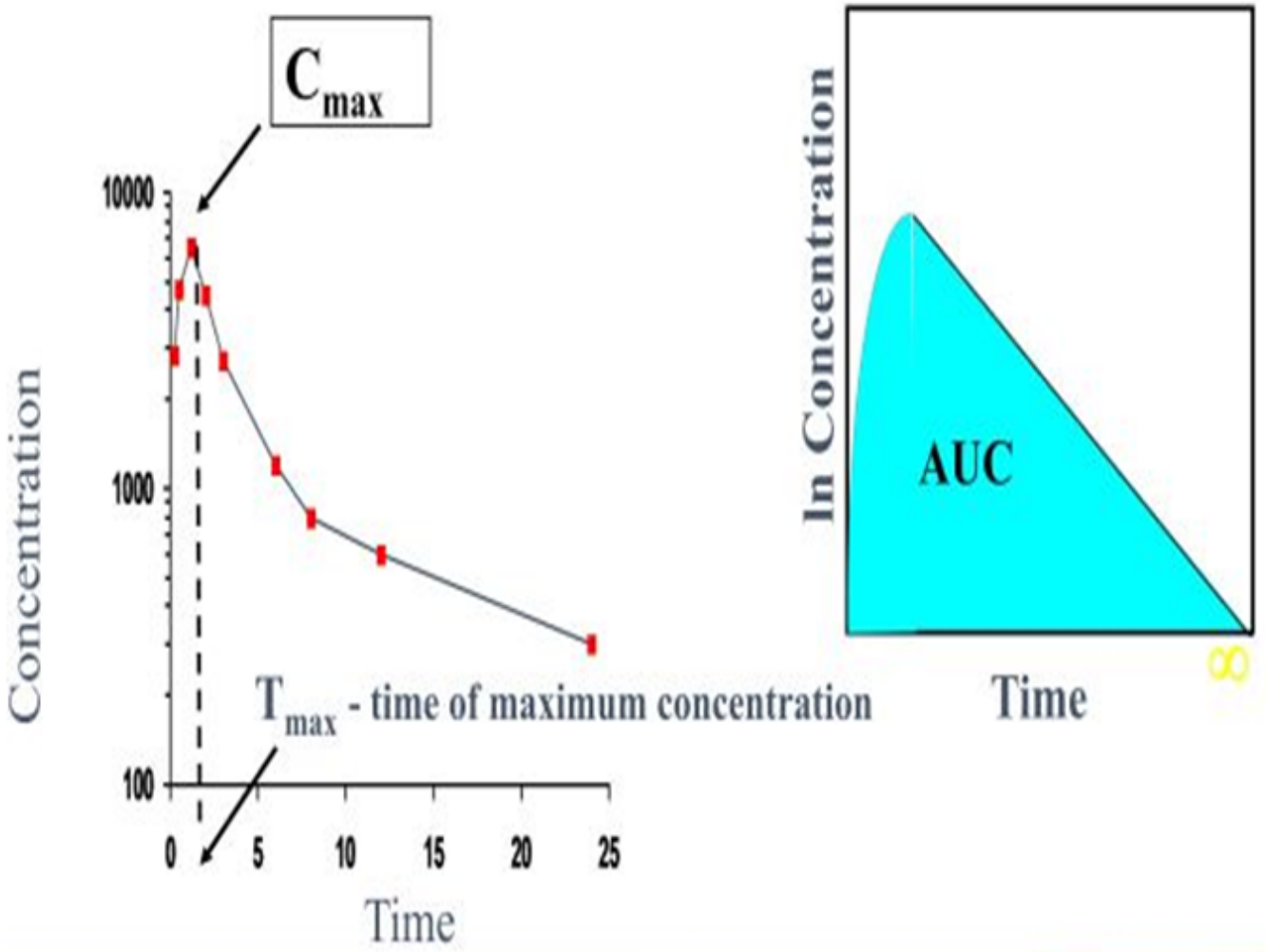
Applicant must use "the most accurate, sensitive, and reproducible approach available" (21 CFR 320.24(b)

Order of preference:

1. PK
2. PD
3. Clinical
4. In vitro

BE STUDY: PK EQUIVALENCE

Plasma concentration-time profile



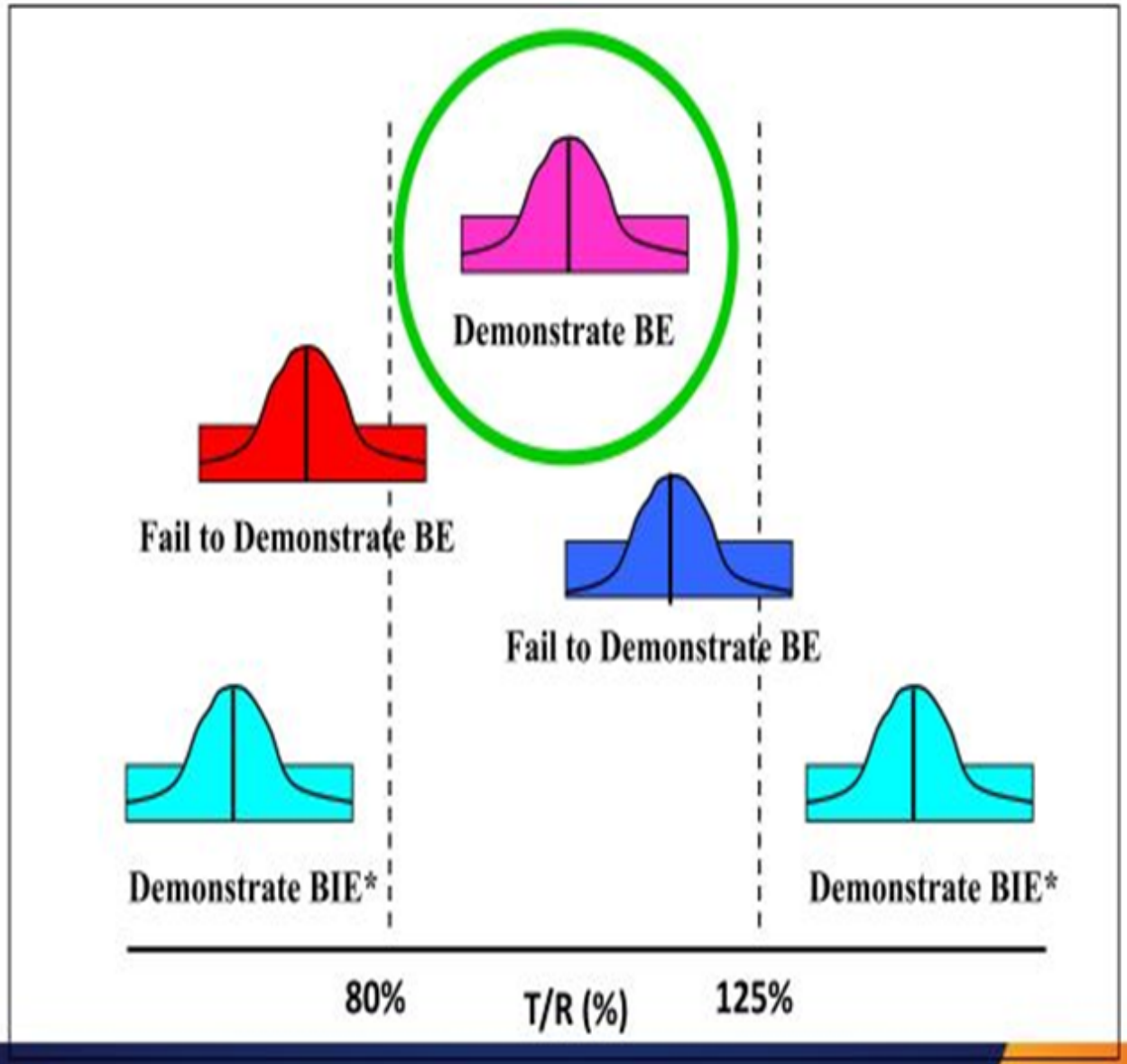
TRADITIONAL APPROACH (PK): Average Bioequivalence (BE) Method

- **Compare** test (T) to reference (R) product
  - Ratio T:R
- **Statistical Approach**/analysis:
  - Cmax - Ratio Cmax (T) to Cmax (R)
  - AUC - Ratio AUC (T) to AUC(R)
  - Statistical inference:
    - 90% confidence intervals using geometric mean ratios, 90% CI of 80 to 125%

Guidance for Industry: Statistical Approaches to Establishing Bioequivalence. https://www.fda.gov/downloads/drugs/guidances/ucm070244.pdf

Guidance for Industry: Bioequivalence Studies with PK Endpoints for ANDAs. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf

POSSIBLE OUTCOMES OF BE STUDIES



*BIE - Bioinequivalence

Traditional BE Approaches
Various issues

Study Designs:

- **Two-period, two-sequence, two-treatment, single dose, crossover (preferred)**
- Parallel vs. non-replicate design
- Group sequential
- Fed vs. fasted
- Healthy volunteer vs. patient
- Single vs. multiple dose

Analysis issues:

- Multiple groups
- Carryover effects
- Outliers
- Dropouts
- Narrow therapeutic index (NTI) drugs
- Use of partial AUCs

Bioequivalence Studies with Pharmacokinetic Endpoints for drugs submitted under an ANDA Guidance: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf
Jiang W, et al. AAPS J 2015. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4476992/

Average BE Approaches Breaks Down When…

- Drug products have negligible systemic uptake
  - Cannot measure drug concentrations
- Site of action is local
  - Inhaled, dermal, locally acting GI/GU/GYN
- No identified PK (or PD) measure

- FDA recommends "Comparative clinical endpoint BE study" –
  - Comparative clinical study in humans
  - Clinical PD study
- PLUS other data

Comparative Clinical Endpoint BE Study

STUDY DESIGN

- Patients
- Multiple doses
- Biomarker
- Test vs. Reference vs. Placebo
- Primary endpoint
- 90% CI T to R
- (M)ITT, Observed Per Protocol (PP), safety population

CHALLENGES

- Multiple treatment indications
- Time of measurement may not be sensitive to detect difference between products
- Identifying predictable and sensitive PD measure
- Impact of disease variability
- Subjective and variable rating scale
- **Large** sample size
- **Lengthy**
- **Expensive**
- Less reproducible
- Poorly conducted
- Insensitive indicator of BE
- No Product Specific Guidance (PSG)

Comparative Clinical Endpoint BE Study

STUDY CONDUCT

- Patients
- Biomarker
- Multiple doses
- Test vs. Reference vs. Placebo
- Primary endpoint
- 90% CI T to R
- (M)ITT, Observed Per Protocol (PP), safety population

CHALLENGES

- Multiple treatment indications
- Time of measurement may not be sensitive to detect difference between products
- Identifying predictable and sensitive PD measure
- Impact of disease variability
- Subjective and variable rating scale
- Large sample size
- Lengthy
- Expensive
- Less reproducible
- **Poorly conducted**
- **Insensitive indicator of BE**
- No Product Specific Guidance (PSG)

Question:

Can we advance the science and technology such that comparative clinical endpoint BE studies may not be needed for products where relevant systemic BE cannot be demonstrated???

OUTLINE

- Generic Drugs and OGD 101
- Bioequivalence
  - Traditional approaches
- **Newer approaches**

LEVERAGING GDUFA REGULATORY SCIENCE

Developing "New approaches" for "sameness"/Equivalence

PRE-GDUFA

GDUFA I

- Mandated GDUFA Regulatory Science program
- Modest size ($100M)
- ~100 grants/contracts
- Published ~800 PSGs, 40% for complex generic drug products
- Created foundational elements for GDUFA II

GDUFA II

- Continue GDUFA Regulatory Science program
- Creates timelines to publish PSGs for non -complex NMEs
- Establishes Pre-ANDA program for complex generic drug products

GDUFA REGULATORY SCIENCE PROGRAM

- Huge Success Story
- Spectacular return on investment for industry related to
  - development
  - regulation and
  - review
- Evidence-, research- and science-based standards setting program

OUTCOMES:

1. Provides information for industry on HOW to develop, i.e., standard setting/Guidance (PSGs)

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

2. Assists FDA reviewers and scientists when evaluating ANDA
3. ANDA approvals

COMPLEX GENERIC DRUG PRODUCTS

Formally defined in GDUFA II Commitment Letter:

- **Complex Mixtures**
  - Peptides, polymeric compounds, complex mixtures of APIs, naturally sourced ingredients
- **Complex formulations**
  - Liposomes, colloids
- **Complex Routes of Delivery**
  - Locally acting such as dermatologic products and complex ophthalmologic and otic products that are formulated as suspensions, emulsions or gels
- **Complex Dosage Forms**
  - Transdermals, MDI, extended release injectables
- **Complex drug-device combination products**
  - Autoinjectors, MDI
- Other products where complexity or uncertainty would benefit from early scientific engagement

GDUFA II "Goals" or "Commitment" letter: http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/ucm525234.pdf

Complexity of Orally Inhaled & Nasal Drug Products (OINDP)

Drug State	Site of Action	Dosage Form
Solution	Systemic	Aqueous Spray
	Local	Aerosol Metered
		Aqueous Spray
Suspension	Local	Aqueous Spray
		Aerosol Metered
Solid blend	Systemic	Powder
	Local	Powder

Complexity of Orally Inhaled & Nasal Drug Products (OINDP)

Drug State	Site of Action	Dosage Form
Solution	Systemic	Aqueous Spray
	Local	Aerosol Metered
		Aqueous Spray
Suspension	Local	Aqueous Spray
		Aerosol Metered
Solid blend	Systemic	Powder
	Local	Powder

Complexity of Orally Inhaled & Nasal Drug Products (OINDP)

Drug State	Site of Action	Dosage Form
Solution	Systemic	Aqueous Spray
	Local	Aerosol Metered
		Aqueous Spray
Suspension	Local	Aqueous Spray
		Aerosol Metered
Solid blend	Systemic	Powder
	Local	Powder

Complexity of Orally Inhaled & Nasal Drug Products (OINDP)

Drug State	Site of Action	Dosage Form
Solution	Systemic	Aqueous Spray
	Local	Aerosol Metered
		Aqueous Spray
Suspension	Local	Aqueous Spray
		Aerosol Metered
Solid blend	Systemic	Powder
	Local	Powder

COMPLEX GENERIC DRUG PRODUCTS

We can resolve the "sameness" or equivalence challenges with the scientific foundations generated via GDUFA Regulatory Science Program by:

- Determining key factors controlling BE for various drug product types
- Identifying failure modes for BE relevant to drug product complexity
- Developing and validating novel, relevant, sensitive, and efficient approaches to assess "sameness" and equivalence

CHALLENGES FOR COMPLEX GENERIC DRUG PRODUCTS

Pharmaceutical Equivalence

- How to demonstrate active ingredient "sameness"?
- What is the role of and how to understand process and product controls?
- Can we characterize complex API?
- Can we identify, characterize and measure critical quality attributes of drug product formulations?

Therapeutic Equivalence

- What kinds of comparative analyses are needed to support substitution?
  - What is the intended clinical response for which the RLD was designed?
  - For drug-device combination products, what differences in the device are allowable?
  - How to understand the patient interface/use with the final drug product?
- Are the inactive ingredients (or excipients), if different from RLD, allowable?

CHALLENGES FOR COMPLEX GENERIC DRUG PRODUCTS

Bioequivalence

- When straightforward BE (systemic PK) approach not applicable, how can BE be measured?
- Can we improve methodologies for BE assessment?
- Can we develop sensitive and validated ways to demonstrate BE?
- How can we leverage our knowledge of PE to assist with BE??

NEWER APPROACHES

1. Better understanding of product performance attributes
2. New Study Designs and Statistical Approaches
3. Clinical Pharmacology tools

ALL WITH THE INTENT TO.....
compile and align
orthogonal evidence
to conclude
"sameness"/Equivalence
using a
"Weight of Evidence Approach"

NEWER APPROACHES

1. Better understanding of product performance attributes
2. New Study Designs and Statistical Approaches
3. Clinical Pharmacology tools

ALL WITH THE INTENT TO.....
compile and align
orthogonal evidence
to conclude
"sameness"/Equivalence
using a
"Weight of Evidence Approach"

BETTER UNDERSTING DRUG PRODUCT PERFORMANC ATTRIBUTES

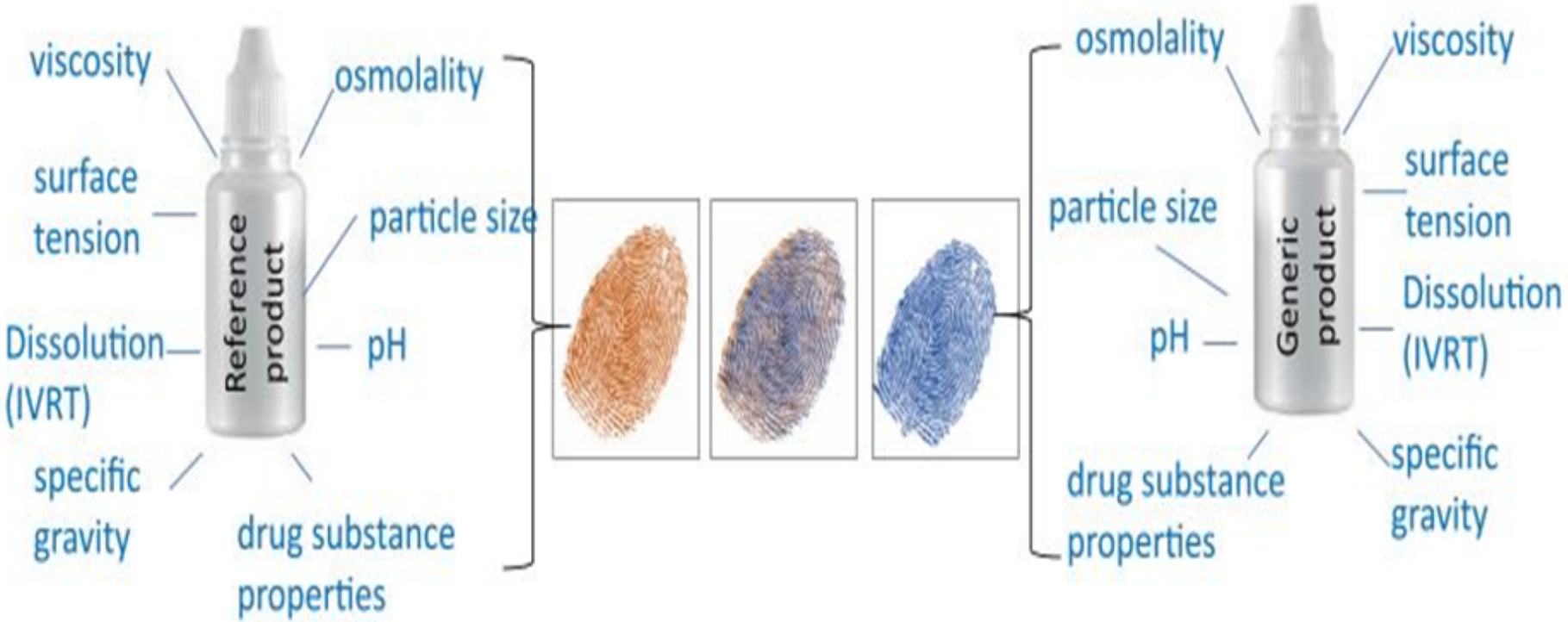
- As the complexity of the dosage form increases, so do the failure modes for "sameness" (or equivalence)
- Can we systematically mitigate the risks of failure modes?
- Can we leverage knowledge of PE?

- Understanding the arrangement of matter in the drug formulation
  - Physical and structural property "sameness"
- Using *in vitro* testing methodologies
  - Release testing (IVRT)
  - Permeation testing (IVPT)
  - Microsampling strategies
  - Raman spectroscopy
  - Computational fluid dynamics (CFD)
  - Earth Movers Distance
  - Others

EXAMPLE: Ophthalmic Formulations

Physicochemical "sameness"

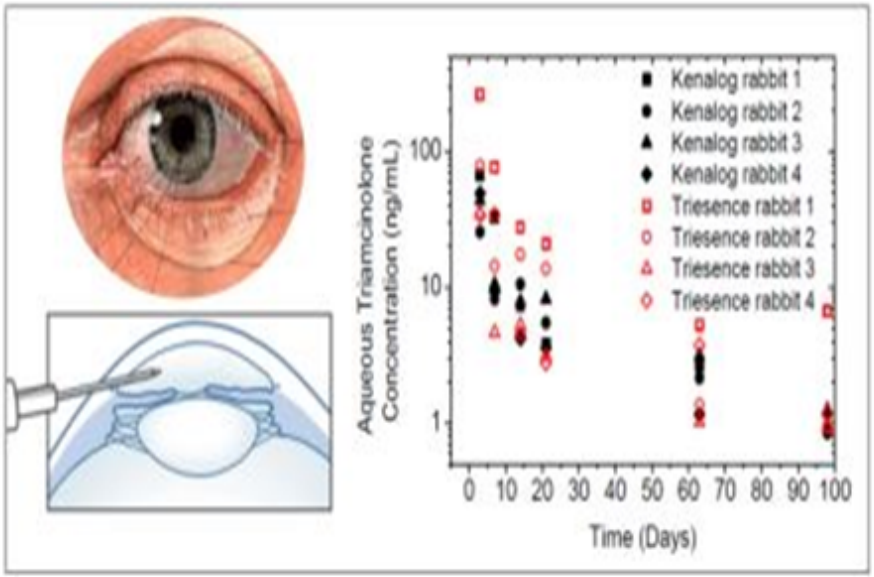
Plus comparable in vivo bioavailability



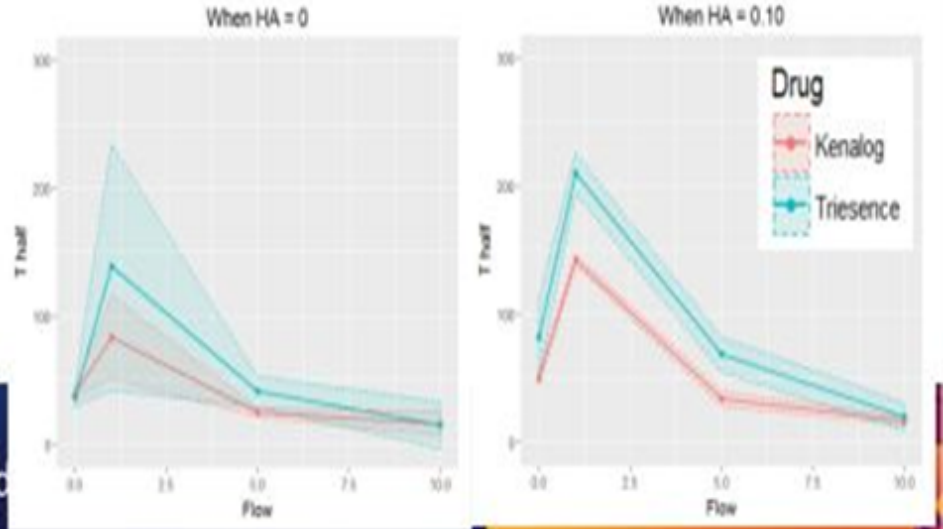
*A product that meets Q1/Q2 sameness, comparability of physicochemical properties, and an acceptable comparative in vitro release rate should become available at the site of action at a rate and to an extent that is not significantly different from that of the RLD, thus meeting the requirement for demonstrating bioequivalence.FDA-2014-P-2301, FDA-FDA-2016-P-2781, FDA-2016-P-2782

EXAMPLE: Ophthalmic triamcinolone acetonide

- Aqueous humor PK BE study:
  - Requires sparse sampling (single sample per subject)
  - Large study population and statistical bootstrapping
  - Small aqueous humor PK study was inconclusive due to high variability



- In vitro tests can assess formulation or manufacturing differences to support BE
  - Optimized in vitro release testing (flow rate and hyaluronic acid (HA)) can differentiate between two formulations



FDA grant 1U01FD005173-01 PI: Prof. M. Sailor (UCSD)

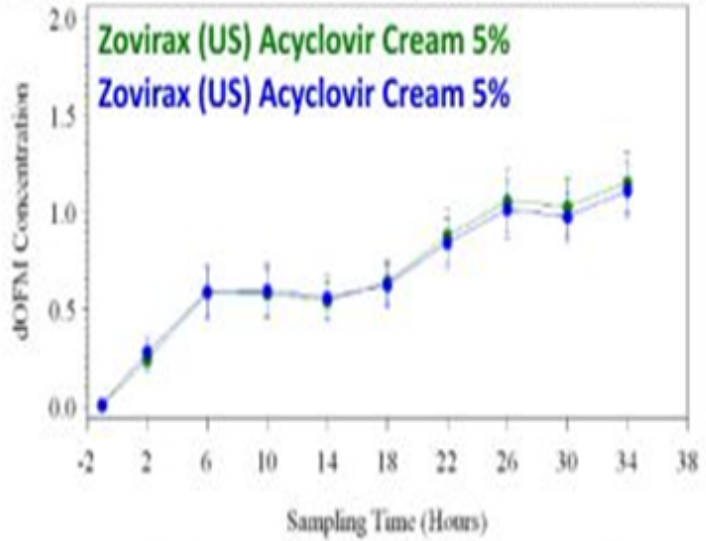
NEWER APPROACHES

1. Better understanding of product performance attributes
2. **New Study Designs and Statistical Approaches**
3. Clinical Pharmacology tools

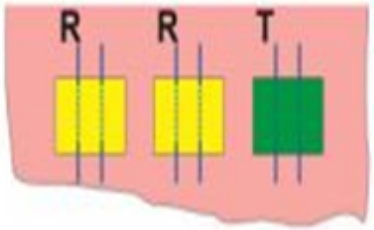
ALL WITH THE INTENT TO.....
compile and align orthogonal evidence to conclude "sameness"/Equivalence using a "Weight of Evidence Approach"

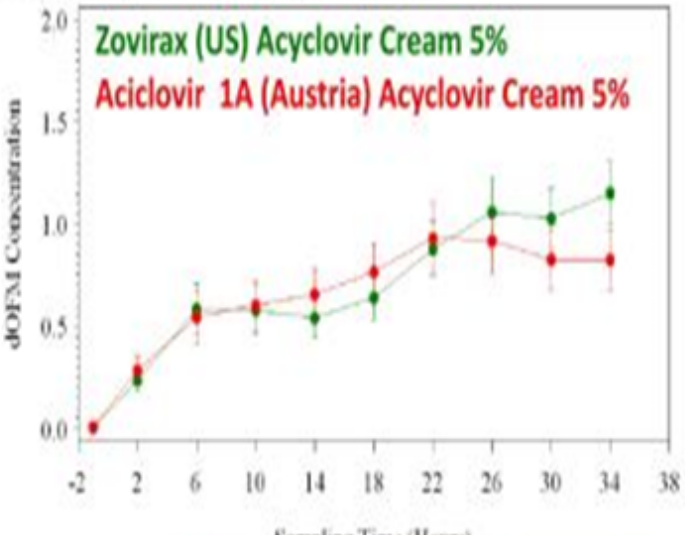
EXAMPLE: Alternative In Vivo BE Approaches
Topical Products

Open Flow Microperfusion -- direct measurement of drug in skin



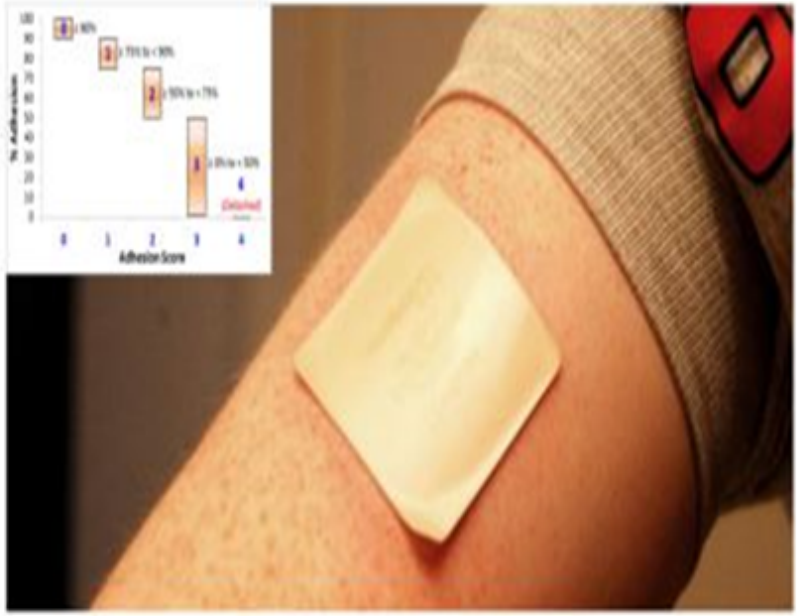
Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]
log(C_{max})	[-0.155 ; 0.190] or [85.7 % ; 120.9%]





Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]
log(C_{max})	[-0.498 ; 0.022] or [60.8 % ; 102.2%]

EXAMPLE: New Statistical Designs
Transdermal System (TDS) Adhesion



- Generic TDS require adhesion testing to demonstrate same clinical effect
- Improvements in adhesion technology over time
  - Low power for well adhering products
  - Required large number of subjects

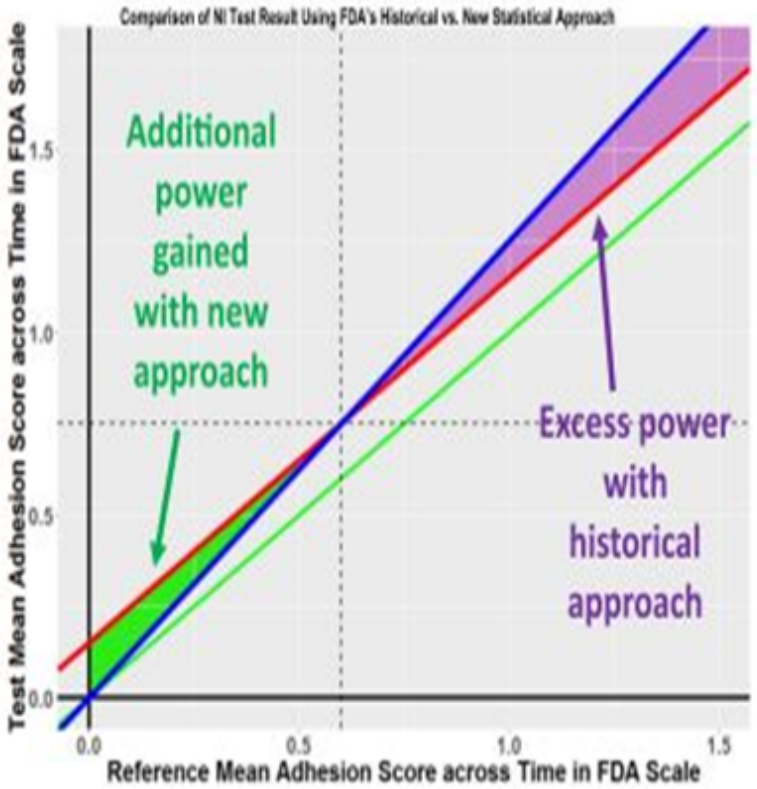
Question: Can we improve study design, including statistical & analytical plan?

- Multidisciplinary use of QMM

FIGURE SOURCE: https://en.wikipedia.org/wiki/Transdermal_patch (Free Media)

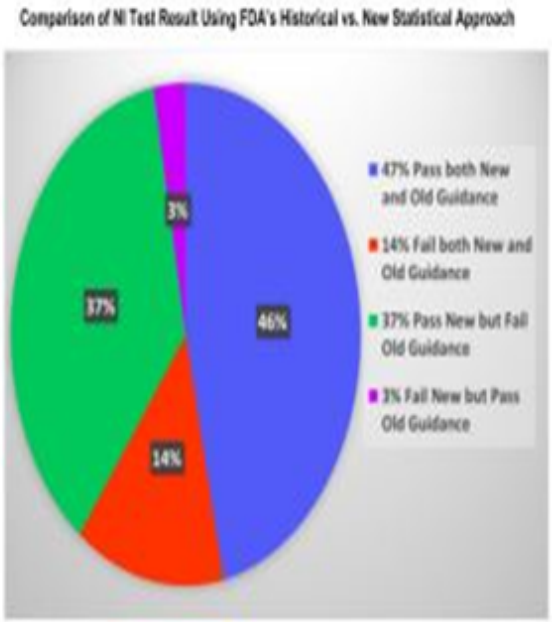
EXAMPLE: New Statistical Designs
Transdermal System (TDS) Adhesion

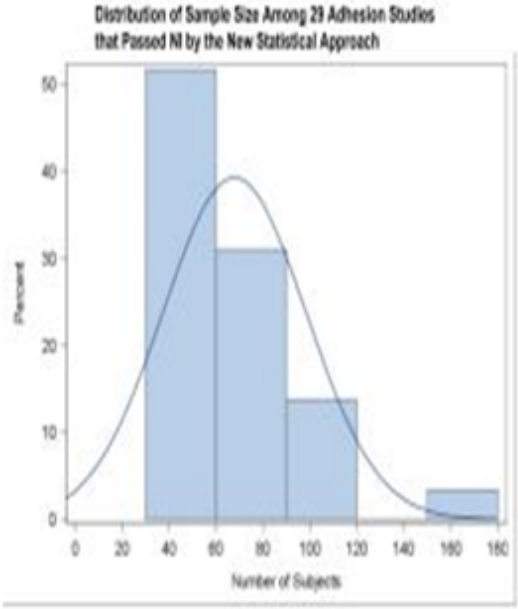
- Improved statistical approach using "difference-of-means" (DOM) non-inferiority test (revised Guidance (PSG*)) vs. historical ratio of means NI testing
- Effectively corrected low power for well adhering TDS



*https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM504157.pdf

EXAMPLE: New Statistical Designs
Transdermal System (TDS) Adhesion





Conclusion:

- Review of ANDAs using "new" approach reveals **enhanced approvability** of well adhering TDS generic drug products
- Significantly **reduces sample size**
  - From ~1,000 to < 200 study subjects
- **ANDAs approved**

NEWER APPROACHES

1. Better understanding of product performance attributes
2. New Study Designs and Statistical Approaches
3. **Clinical Pharmacology tools**

ALL WITH THE INTENT TO.....
compile and align
orthogonal evidence
to conclude
"sameness"/Equivalence
using a
"Weight of Evidence Approach"

CLINICAL PHARMACOLOGY TOOLKIT

Leveraging Quantitative Methods

NEW DRUGS

- PK-PD modeling
- Exposure-response analysis
- Clinical trial simulation
- Population PK

GENERIC DRUGS

- Same – core of BE assessment
  (can have complicated model development for "sameness", e.g., **pAUCs**)
- Narrow Therapeutic Index
- Virtual BE study
- **PBPK**
- Model-based BE assessment for drugs with sparse PK
- **Modeling & Simulation (QMM)**

PARTIAL AUC (pAUC)

- Not only for drugs with long terminal elimination half-life
- Need a good understanding of the RLD
- What is the intended therapeutic effect? When does it occur?
- Can pAUCs be used relevant to the various occurrences of the intended therapeutic effect?
- Other uses for pAUC with generics

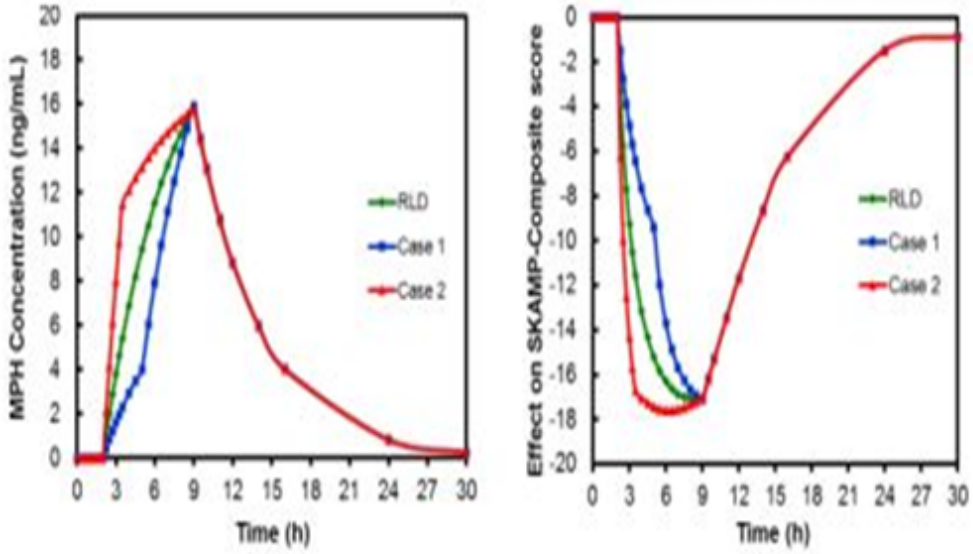
Use of Partial AUCs
EXAMPLE: *Transdermal methylphenidate*

- Methylphenidate Transdermal system (MPH TDS) is indicated for ADHD in children and adolescents
  - Applied once daily for 9 hours with effectiveness sustained for 10 to 12 hours
  - RLD has a lag time of ~2 hours; apply 2 hours before effect needed
  - SKAMP composite score (PD) correlates with therapeutic effect
  - Critically of the onset, duration, and offset of therapeutic effect
    - School performance, after school (homework) balanced with appetite and sleep

Question: Could pAUC be recommended as a metric for BE?

Use of Partial AUCs
EXAMPLE: *Transdermal methylphenidate*

- PK/PD data were simulated for the RLD TDS and 2 hypothetical TDSs, i.e., formulation varies (with similar Cmax and AUC but different $pAUC_{2\text{-}9hr}$ as compared to RLD;
- PD responses ([SKAMP]-Composite score) are predicted to be different for the two hypothetical TDSs.



- **Conclusion:** pAUC2-9h, in addition to conventional Cmax and AUC metrics, has been recommended in the Guidance (PSG) to discern any clinically relevant differences in efficacy

Use of Partial AUCs
EXAMPLE: *Abuse-Deterrent Opioids*

Oral and nasal PK studies are recommended to evaluate the abuse deterrence of the proposed generic vs. RLD when physically manipulated or chewed

NDA #	API	Trade Name	Dosage Form	In vivo PK AD studies	pAUC recommendation
022272	Oxycodone HCl	**OxyContin**	ER Tablet	IN	$pAUC_{0-8h}$ $pAUC_{0-4h}$
022321	Morphine Sulfate; Naltrexone HCl	**Embeda**	ER Capsule	IN, Oral (crushing)	$pAUC_{0-8h}$
206627	Hydrocodone Bitartrate	**Hysingla ER**	ER Tablet	IN, Oral (chewing)	$pAUC_{0-8h}$ $pAUC_{0-4h}$
206544	Morphine Sulfate	**MorphaBond ER**	ER Tablet	IN	$pAUC_{0-8h}$ $pAUC_{0-4h}$
208090	Oxycodone	**Xtampza ER**	ER Capsule	IN, Oral (chewing and/or crushing)	$pAUC_{0-8h}$ $pAUC_{0-4h}$
208603	Morphine Sulfate	**Arymo ER***	ER Tablet	IN	$pAUC_{0-8h}$ $pAUC_{0-4h}$
209777	Oxycodone HCl	**RoxyBond**	Tablet	IN	$pAUC_{0-8h}$ $pAUC_{0-4h}$

IV: intravenous; IN: intranasal

* The intranasal route is not approved until 2018 due to market exclusivity of MorphaBond

Use of Partial AUCs
EXAMPLE: *Abuse-Deterrent Opioids*

Oral and nasal PK studies are recommended to evaluate the abuse deterrence of the proposed generic vs. RLD when physically manipulated or chewed

Question: What is the clinically relevant PK metrics?

NDA #	API	Trade Name	Dosage Form	In vivo PK AD studies	pAUC recommendation
022272	Oxycodone HCl	**OxyContin**	ER Tablet	IN	$pAUC_{0-\infty}$ $pAUC_{0-t_s}$
022321	Morphine Sulfate; Naltrexone HCl	**Embeda**	ER Capsule	IN, Oral (crushing)	$pAUC_{0-\infty}$
206627	Hydrocodone Bitartrate	**Hysingla ER**	ER Tablet	IN, Oral (chewing)	$pAUC_{0-\infty}$ $pAUC_{0-t_s}$
206544	Morphine Sulfate	**MorphaBond ER**	ER Tablet	IN	$pAUC_{0-\infty}$ $pAUC_{0-t_s}$
208090	Oxycodone	**Xtampza ER**	ER Capsule	IN, Oral (chewing and/or crushing)	$pAUC_{0-\infty}$ $pAUC_{0-t_s}$
208603	Morphine Sulfate	**Arymo ER***	ER Tablet	IN	$pAUC_{0-\infty}$ $pAUC_{0-t_s}$
209777	Oxycodone HCl	**RoxyBond**	Tablet	IN	$pAUC_{0-\infty}$ $pAUC_{0-t_s}$

IV: intravenous; IN: intranasal

* The intranasal route is not approved until 2018 due to market exclusivity of MorphaBond

Use of Partial AUCs
EXAMPLE: *Abuse-Deterrent Opioids*

Conclusion: FDA's PK/PD analysis supports pAUC recommendation for 7 PSGs for abuse-deterrent opioids

- Cmax and AUC: Upper 95% confidence bound ≤ 125.00%
- pAUC as supportive data: Point estimate ≤ 125.00%

NDA #	API	Trade Name	Dosage Form	In vivo PK AD studies	pAUC recommendation
022272	Oxycodone HCl	OxyContin	ER Tablet	IN	$pAUC_{0\text{-}3hr}$, $pAUC_{0\text{-}4hr}$
022321	Morphine Sulfate; Naltrexone HCl	Embeda	ER Capsule	IN, Oral (crushing)	$pAUC_{0\text{-}2hr}$
206627	Hydrocodone Bitartrate	Hysingla ER	ER Tablet	IN, Oral (chewing)	$pAUC_{0\text{-}3hr}$, $pAUC_{0\text{-}4hr}$
206544	Morphine Sulfate	MorphaBond ER	ER Tablet	IN	$pAUC_{0\text{-}3hr}$, $pAUC_{0\text{-}4hr}$
208090	Oxycodone	Xtampza ER	ER Capsule	IN, Oral (chewing and/or crushing)	$pAUC_{0\text{-}3hr}$, $pAUC_{0\text{-}4hr}$
208603	Morphine Sulfate	Arymo ER*	ER Tablet	IN	$pAUC_{0\text{-}3hr}$, $pAUC_{0\text{-}4hr}$
209777	Oxycodone HCl	RoxyBond	Tablet	IN	$pAUC_{0\text{-}3hr}$, $pAUC_{0\text{-}4hr}$

IV: intravenous; IN: intranasal

* The intranasal route is not approved until 2018 due to market exclusivity of MorphaBond

Use of PBPK
EXAMPLE: *Diclofenac Sodium Topical Gel, 1%*

- NSAID indicated for the relief of the pain of osteoarthritis of joints amenable to topical treatment
- Current Guidance (PSG) recommends:
  - *In vivo* BE study with PK endpoints **AND**
  - Comparative clinical BE endpoint study

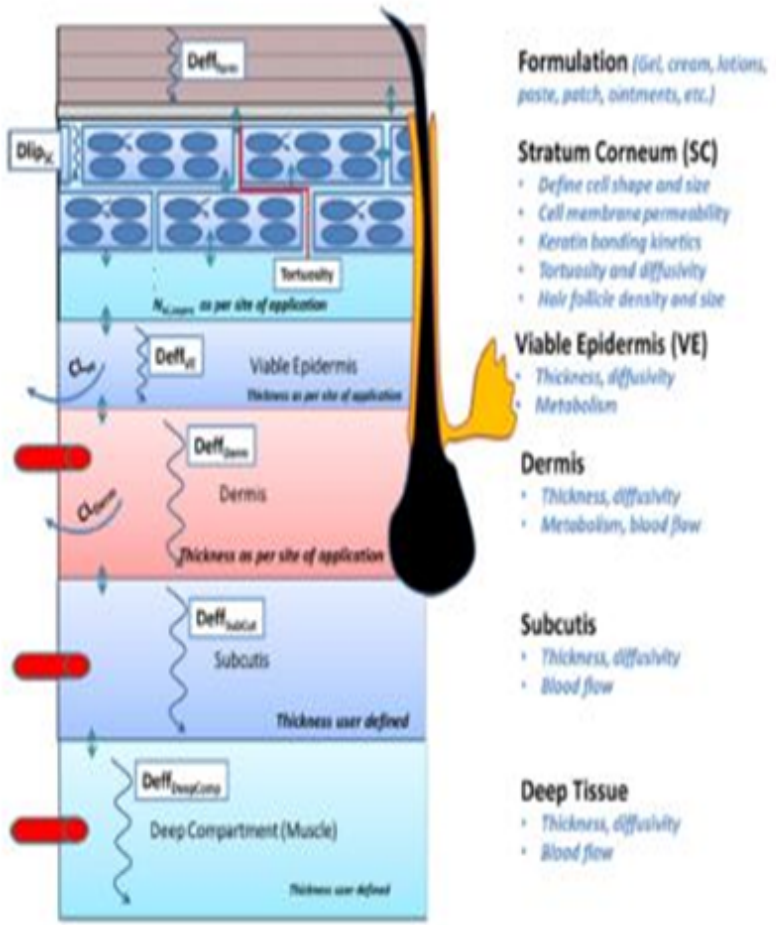
Question: Could an alternate BE approach be acceptable?

Use of PBPK
EXAMPLE: *Diclofenac Sodium Topical Gel, 1%*

Alternate proposal:

- Q1/Q2/Q3 and
- *in vitro* release test (IVRT) and
- *in vivo* BE study with PK endpoints and
- Dermal PBPK model

Conclusion: A suitably verified PBPK model can be used to predict both systemic and local PK for a topically applied gel product and support the BE assessment.



MODELING & SIMULATION (QMM) OPPORTUNITIES FOR GENERICS

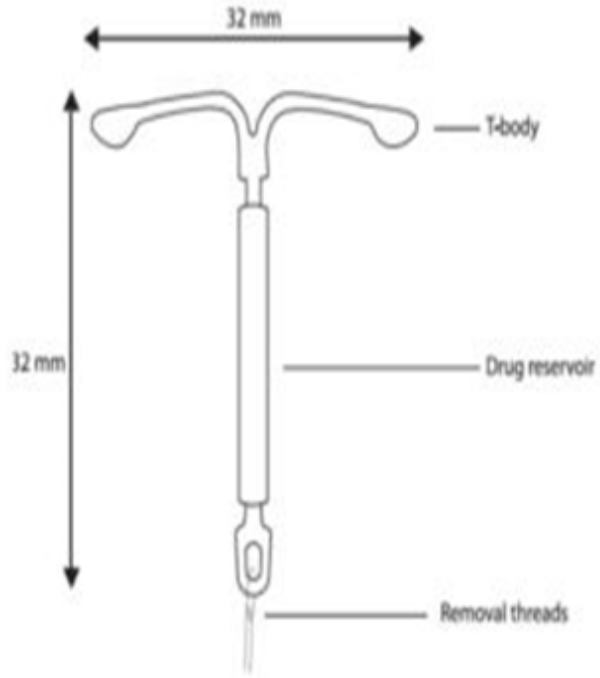
For generic drug development, review and regulatory decision making:

1. **LEVERAGE** knowledge and experience in new drug space
2. Identify **BEST PRACTICES** to improve the use and acceptance of QMM

MODERNIZE
INNOVATE
INTEGRATE

Modeling & Simulation
EXAMPLE: *Levonorgestrel Intrauterine System*

- Levonorgestrel (LNG) Intrauterine System is indicated for 5 years for prevention of pregnancy (RLD approval 2000, patent exp. 12/2015)
- Delivers 52mg of LNG over a 5-yr period
- Comparative clinical endpoint BE study lasting 5 years has practical implications

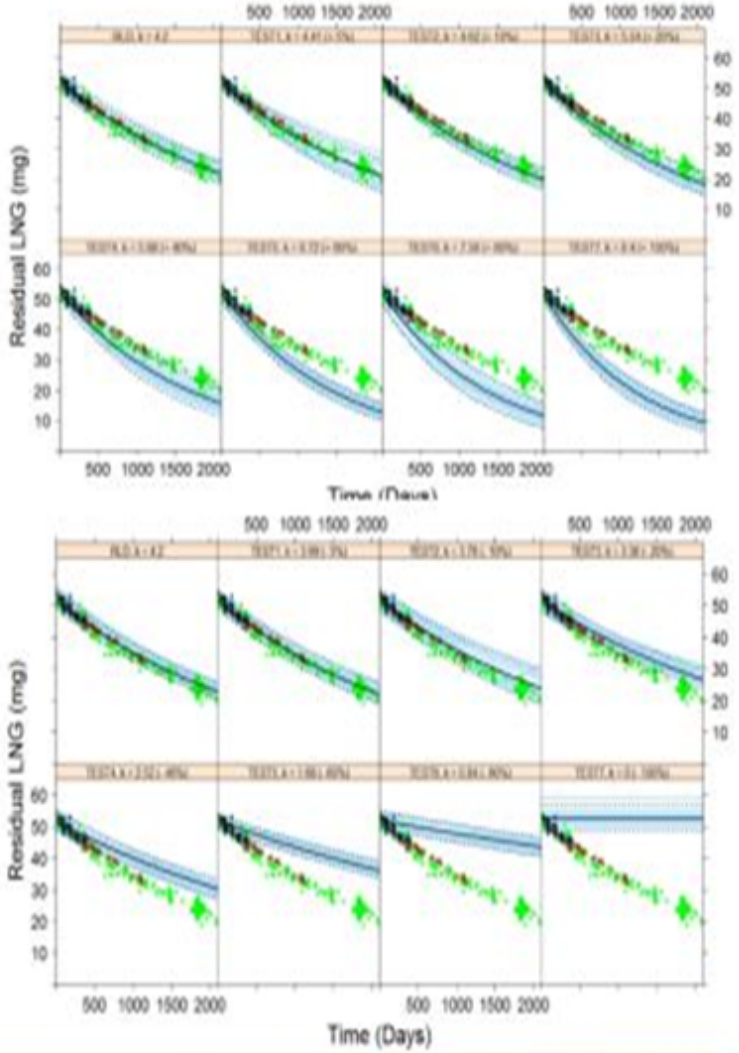


Questions:

1. How to conduct a BE study?
2. Can Modeling & Simulation inform alternative BE study designs including BE metrics and statistical criteria?

Modeling & Simulation
EXAMPLE: *Levonorgestrel Intrauterine System*

- M&S analysis at one-year in vivo BE study
- Create model on rate of drug release
- Model different release rates of LNG vs. RLD
- How well does the model need to perform at Year 1 to predict product will meet standards at Year 5??
  - 90% CI within **95.00-105.26%** for residual LNG at Year 1 would predict therapeutic equivalence across 5 years



Conclusion: A one-year BE study would:

- Significantly shorten generic drug product development time
- Encourage generic competition

Use of Modeling & Simulation
EXAMPLE: *Missing Data in Clinical Endpoint Study*

- ANDA for Brimonidine topical gel
  - Topical treatment of persistent (non-transient) facial erythema of rosacea ≥18yo
- Clinical endpoint BE study was conducted by the ANDA applicant prior to FDA Guidance
- Time points for clinical endpoint assessment differed from Guidance

Question: Can M&S use available data on clinical response to predict response at times recommended in Guidance?

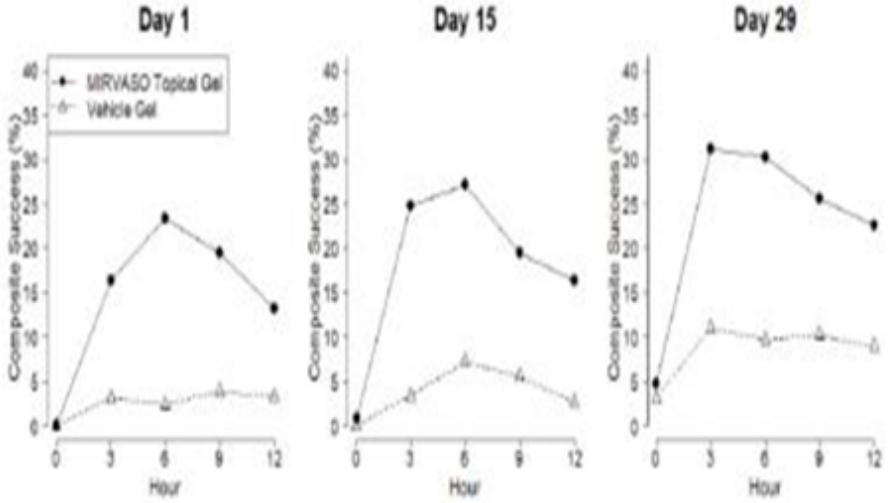
Use of Modeling & Simulation
EXAMPLE: *Missing Data in Clinical Endpoint Study*

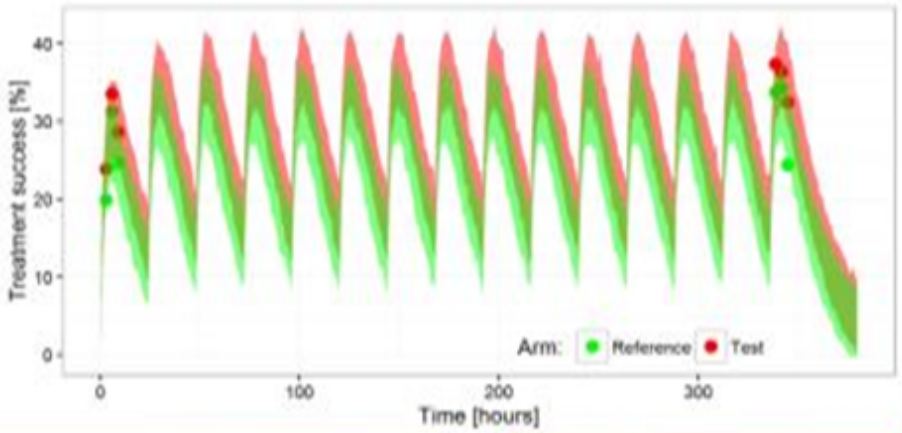
Conclusion: Trial simulations with the validated PK-PD model predicted similar treatment response at Day 15 c/w Day 29

- Visual predictive check (VPC)
- Estimated 90% confidence intervals

- Tentative approval of the ANDA

GUIDANCE ANDA data





Use of Modeling & Simulation
EXAMPLE: *Clinical Impact of PK Differences*

- Naproxen sodium extended-release tablets (NSAID ER)
  - Treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, bursitis, acute gout, primary dysmenorrhea, and the relief of mild to moderate pain

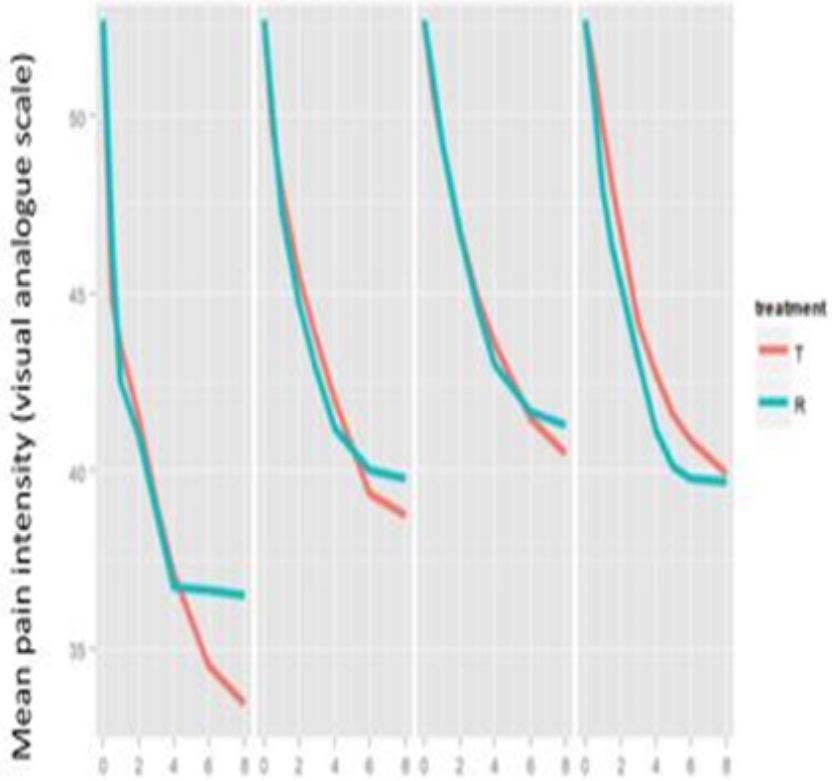
- ANDA - delayed Tmax but similar concentrations c/w RLD

Question: Does Tmax difference have any clinical implications for acute analgesic effect?

Use of Modeling & Simulation
EXAMPLE: *Clinical Impact of PK Differences*

Conclusion: PD simulations predicted that generic and RLD had similar onset of action for acute effect despite Tmax difference

- ANDA supplement was approved



FDA's GENERIC DRUG PROGRAM

- ~1,000 Abbreviated New Drug Applications (ANDA's) submitted/year
- ~10,000 currently approve ANDAs
- ~25% of all ANDAs currently approved were approved since GDUFA, i.e., in the last 6 years

TRANSLATES INTO NUMEROUS OPPORTUNITIES FOR CLIN PHARM TO...

- Identify opportunities
- Develop and validate
- Use and refine
- Lead scientific direction

Clin Pharm Tools useful during:

- Generic drug development
- FDA review/assessment
- Regulatory decision making
- Successful generic drug substitution

OGD Workshops on Complex Generic Drug Products

- October 2-3, 2017: Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review
  - https://www.fda.gov/Drugs/NewsEvents/ucm554182.htm
- October 6, 2017: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations
  - https://www.fda.gov/Drugs/NewsEvents/ucm552461.htm
- October 20, 2017: Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access
  - https://www.fda.gov/Drugs/NewsEvents/ucm557252.htm
- January 9, 2018: New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products
  - https://www.fda.gov/Drugs/NewsEvents/ucm576064.htm
- September 12-13, 2018: Complex Generic Drug Product Development Workshop
  - https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm615104.htm
- October 9-10, 2018 – DIA Workshop on Complex Drug-Device Generic Combination Products

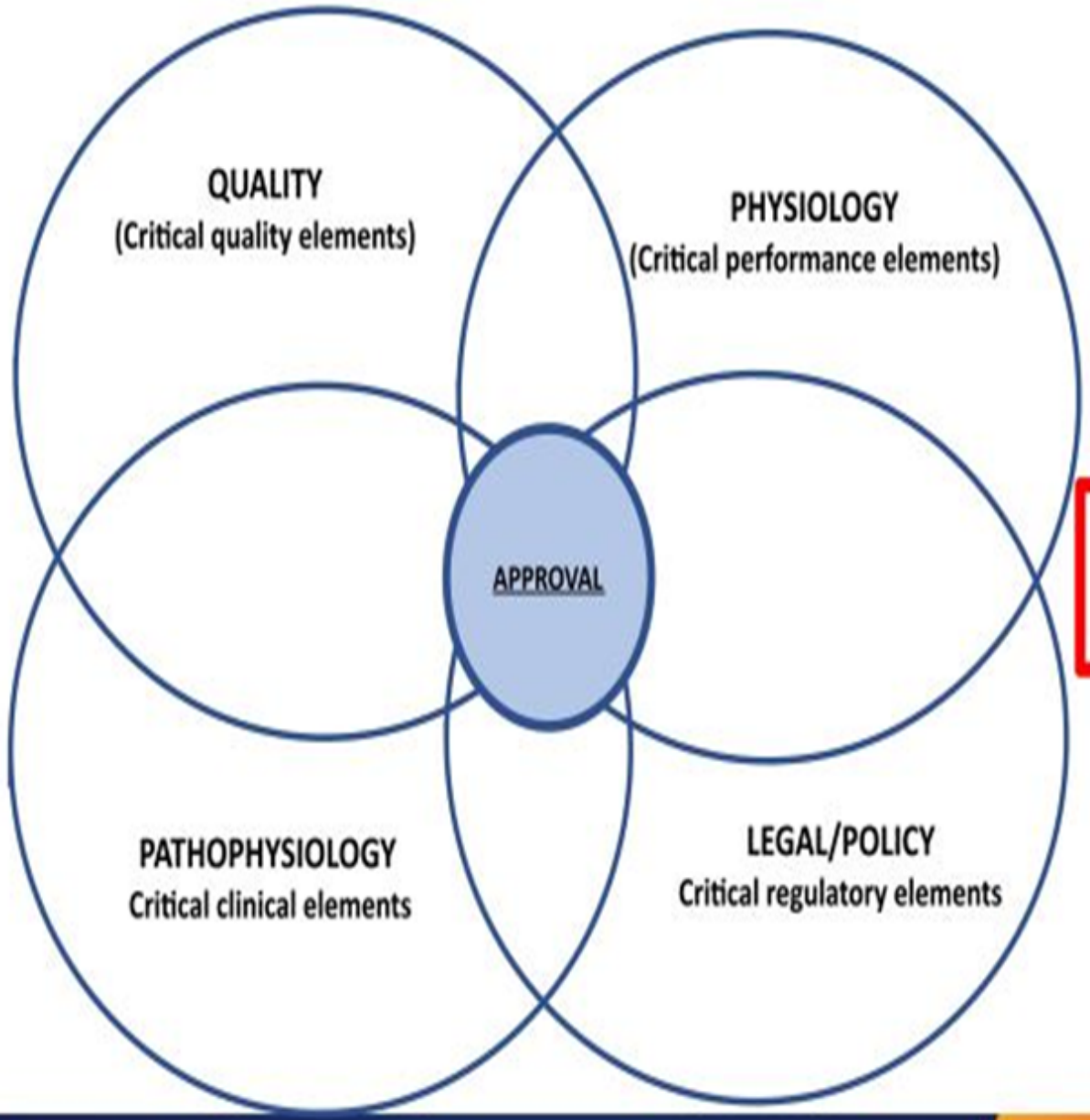
OGD Science, Research & Communication

"Generic Drug Science and Research"

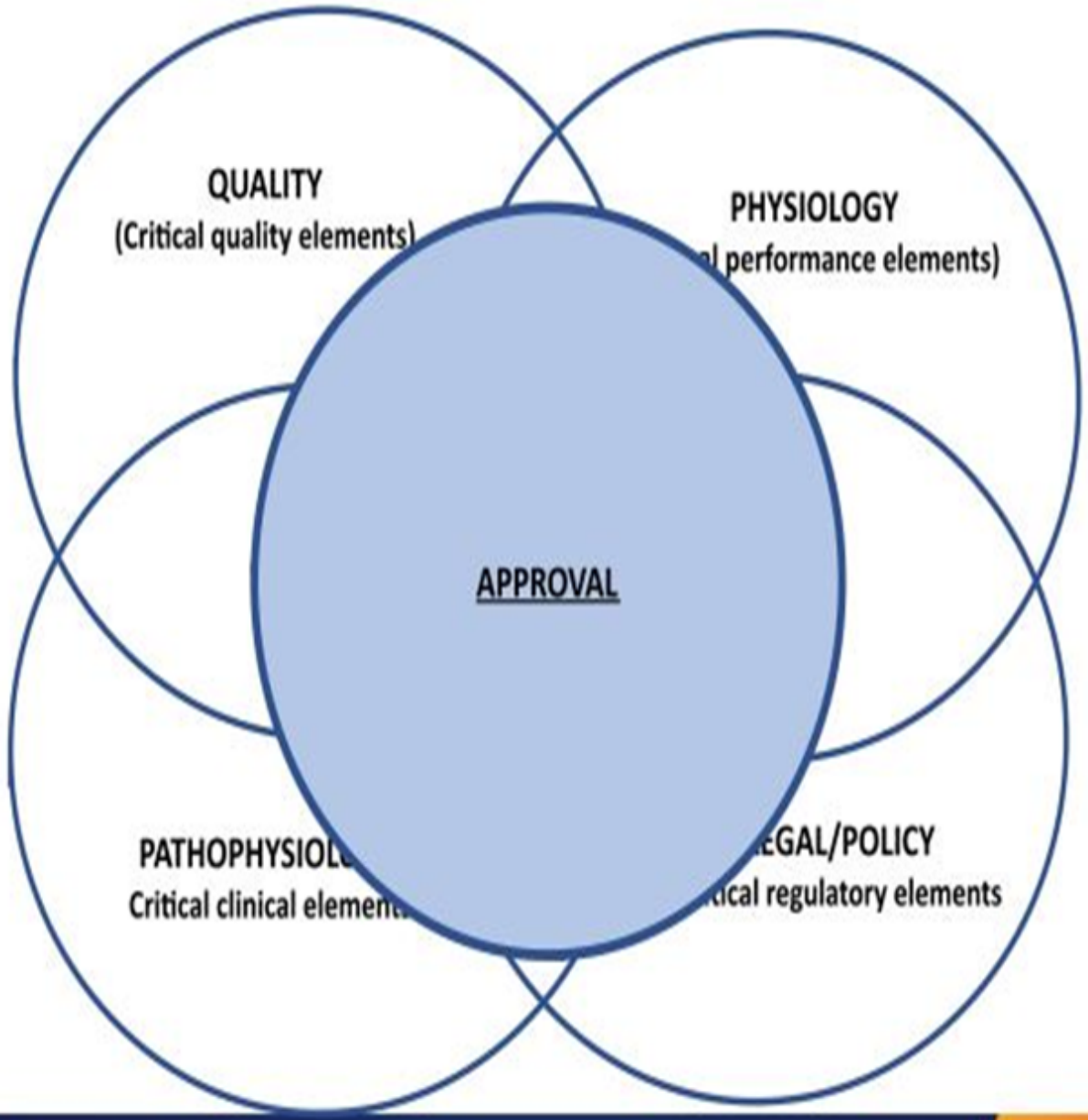
- https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

"Generic Drugs Priorities and Projects" subpage:

- https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm585132.htm



Reverse side of the coin is "failure mode"


QUALITY
(Critical quality elements)
PHYSIOLOGY
l performance elements)
APPROVAL
PATHOPHYSIOL
Critical clinical elemen
EGAL/POLICY
tical regulatory elements

SUMMARY

- Introduced some general principles related to generic drug application (ANDA) requirements
- Reviewed basic BE requirements and traditional approaches
- Highlighted complexities related to generics
- Expanded on newer, more scientific-, research-, and evidence-based approaches used to allow for regulatory review, decision making, and ultimately ANDA approval

- **CONCLUSION:** Bringing high quality, affordable generic medicines to the American public

ACKNOWLEDGMENTS

The incredibly dedicated and talented staff in FDA's Generic Drugs Program

- CDER OGD
  - John Peters
  - Kathryn Amatrudo
  - Ethan Stier
  - Dale Conner
  - Andrew LeBeouf
  - Rob Lionberger
  - Lei Zhang
  - Liang Zhou
  - Jeff Jiang
  - Markham Luke
  - Darby Kozak
  - Sameersingh Raney
  - Kim Witzman
  - Lucy Fang
  - Yan Wang
  - Satish Sharan
- CDER Office of Biostatistics
  - Stella Grosser
  - Wanjie Sun

THANK YOU

Questions

Kathleen Uhl, MD

Director, FDA Office of Generic Drugs

https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm119100.htm

Resources for Industry and Consumers:

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/default.htm