Equivalence of Locally-Acting Drug Products

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GDUFA Research Public Workshop
May 3, 2017

What are Locally-Acting Drugs?

- Drug products not intended to be absorbed into the bloodstream
- The main site of action is local, e.g. the skin, the mucosal surface of the nose or lungs, the eyes, the ears…
- In the past FDA has relied on clinical endpoint bioequivalence studies when no other alternative was available
  - clinical endpoint bioequivalence studies often need large populations and may still not be sufficiently sensitive

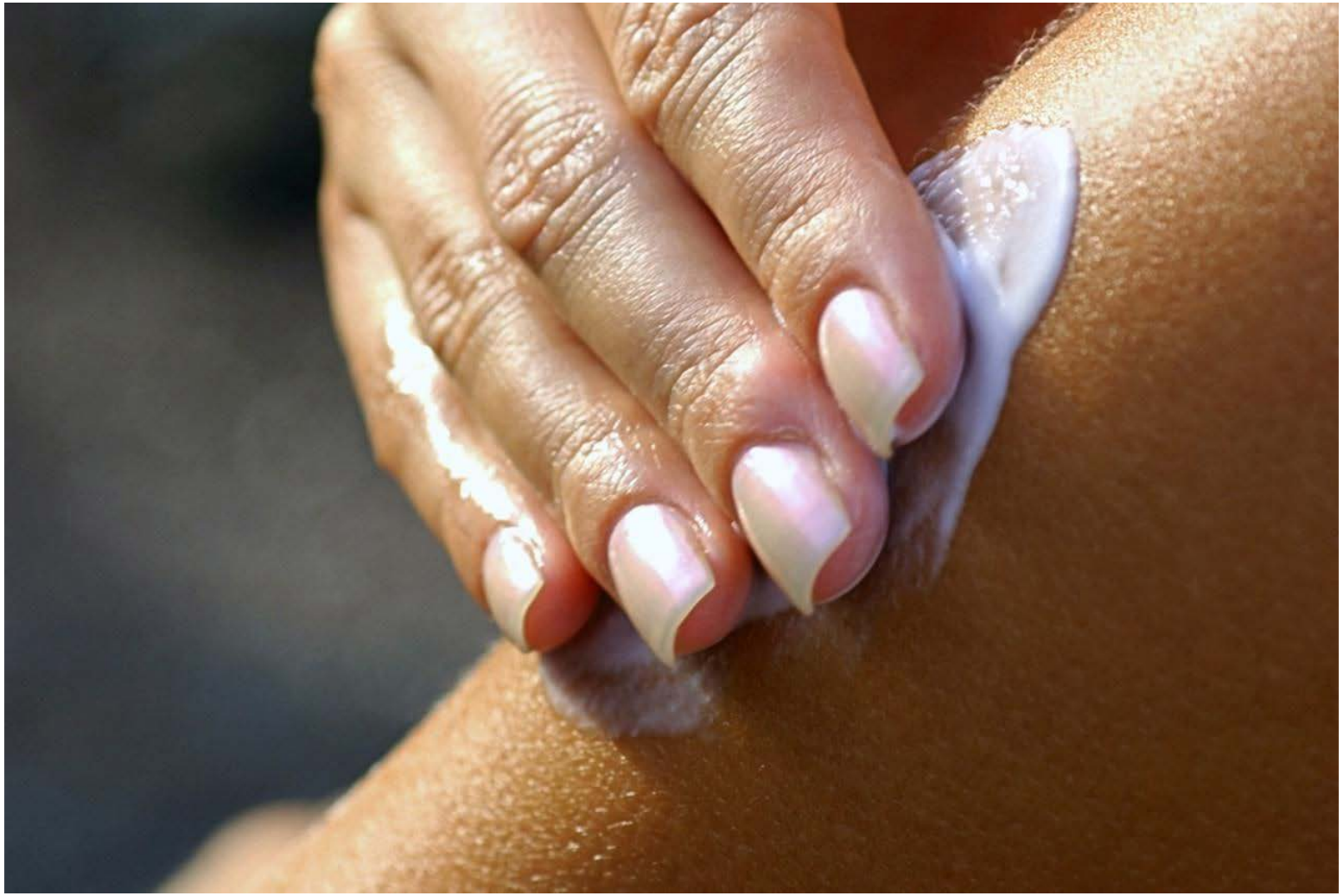
Why Focus on Locally-Acting?

- Relatively fewer generic products for locally-acting drug products
- New technologies may be available to provide new approaches for generic product equivalence

Regulatory Basis for Alternatives

- A 2003 addition to the Federal Food Drug and Cosmetic Act at Section 505(j)(8)(A)(ii) indicates that
  - "For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action".

Skin creams and lotions



Q1 and Q2 and Q3 Definitions

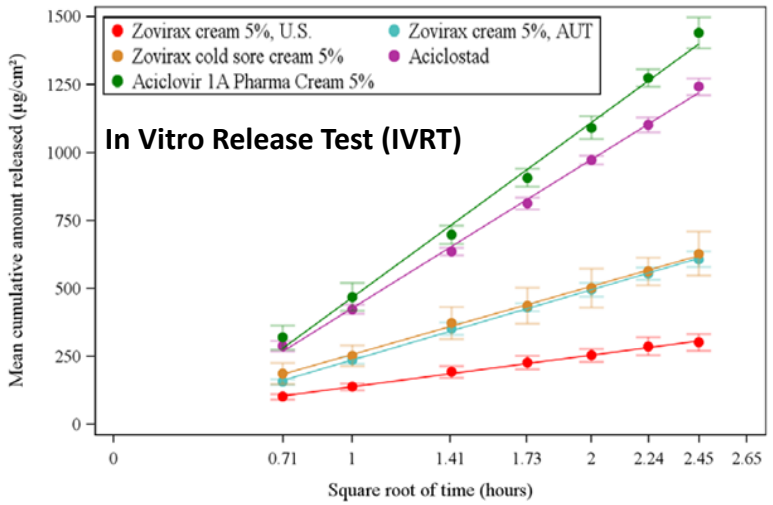
- Classify product similarity
  - Q1: Same components
  - Q2: Same components in same concentration
  - Q3: Same components in same concentration with the same arrangement of matter (microstructure)
    - Q3 is characterization based determination
    - In vitro performance data can support Q3 equivalence or allow small Q3 differences
    - Q3 differences come from manufacturing or excipient sourcing

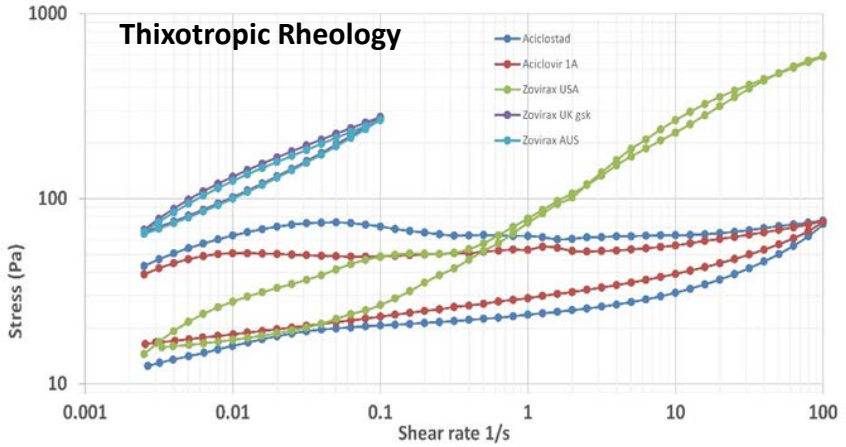
FDA Coordinated Research

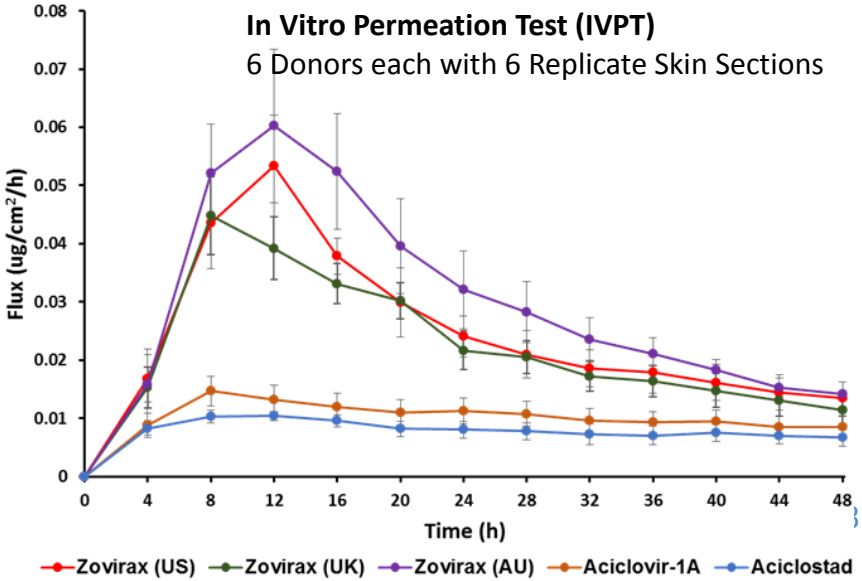
- Six coordinated grants (international: US, Europe, Australia) that include
  - New in vivo data
  - Manufacturing of semi-solid formulations
  - Characterization of semi-solid formulations
  - New PBPK modeling approaches
- Advance Q3 Equivalence
  - Guidance to generalize approach
- Open Flow Microdialysis
  - Dermal insertion of semipermeable tube

Acyclovir Cream 5%

	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS	[redacted]	[redacted]
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
	[redacted]	Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8	2.5	3.4	6.8	6
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95







In Vivo Dermal Microdialysis (dOFM)

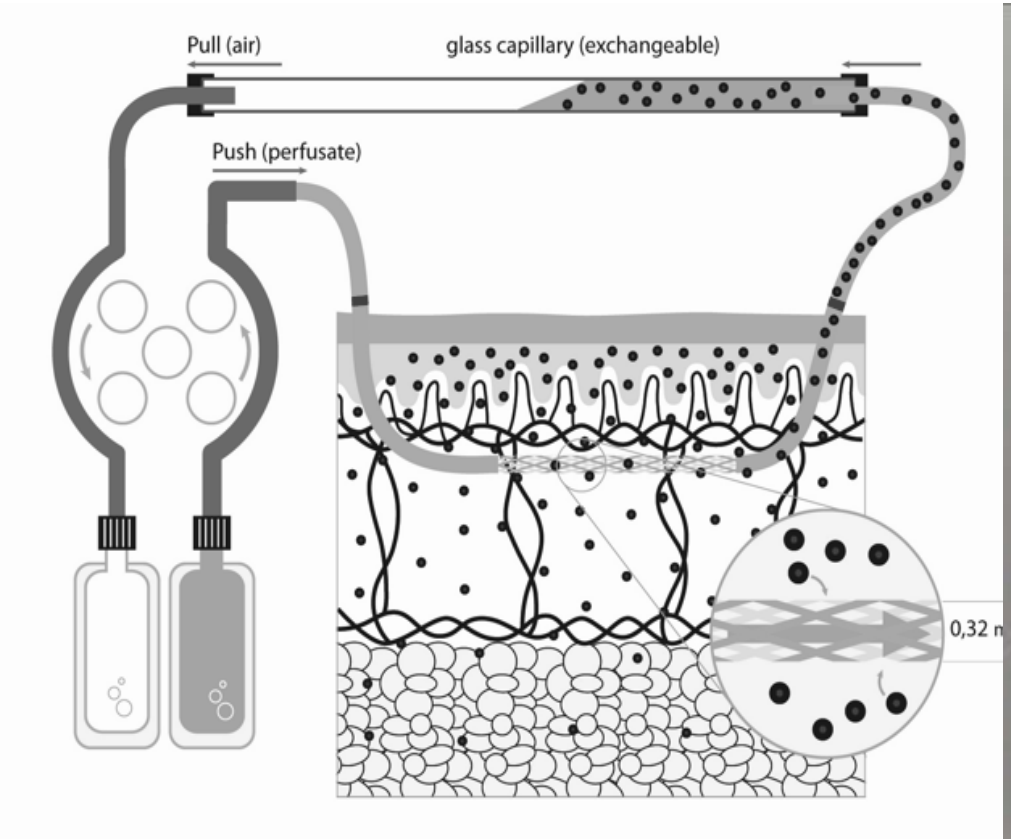
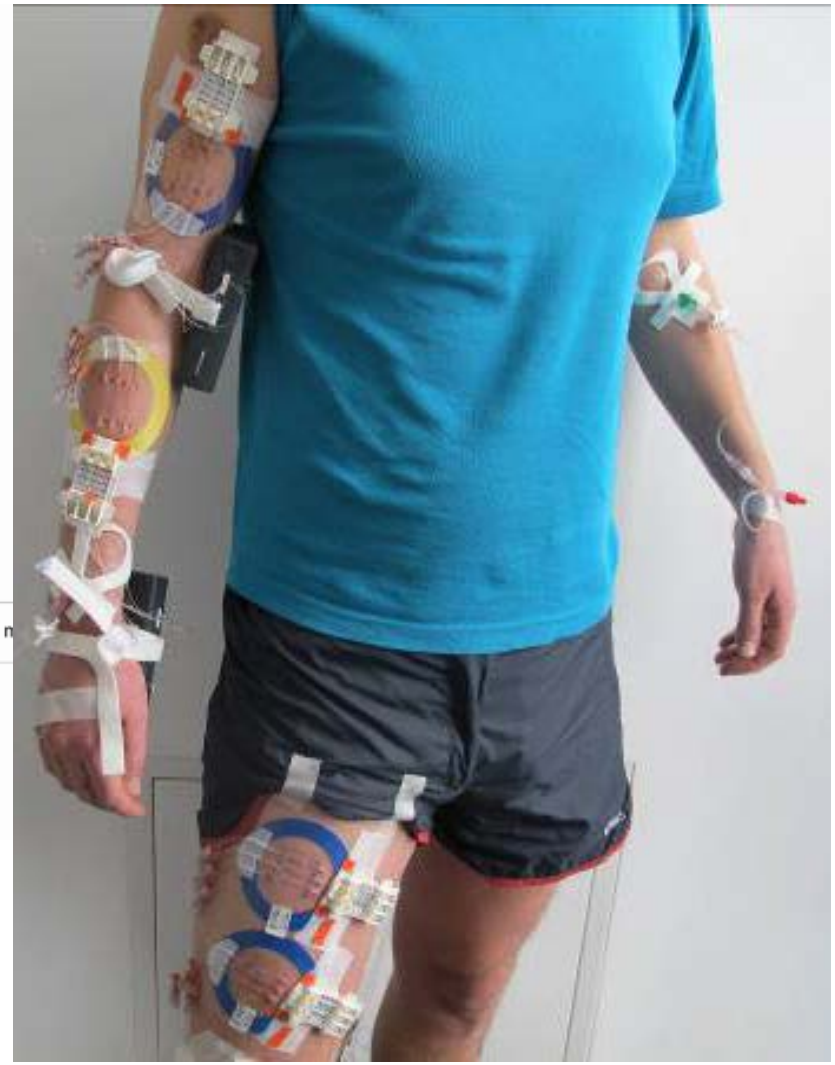
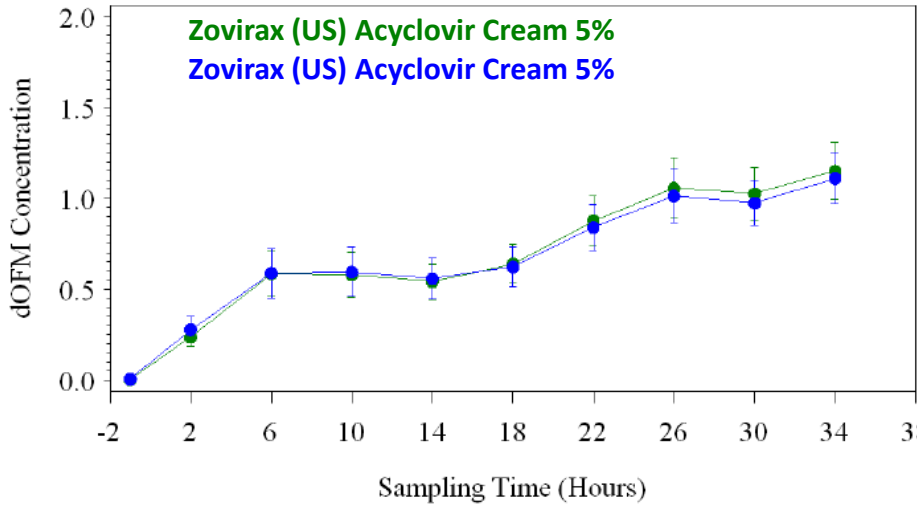


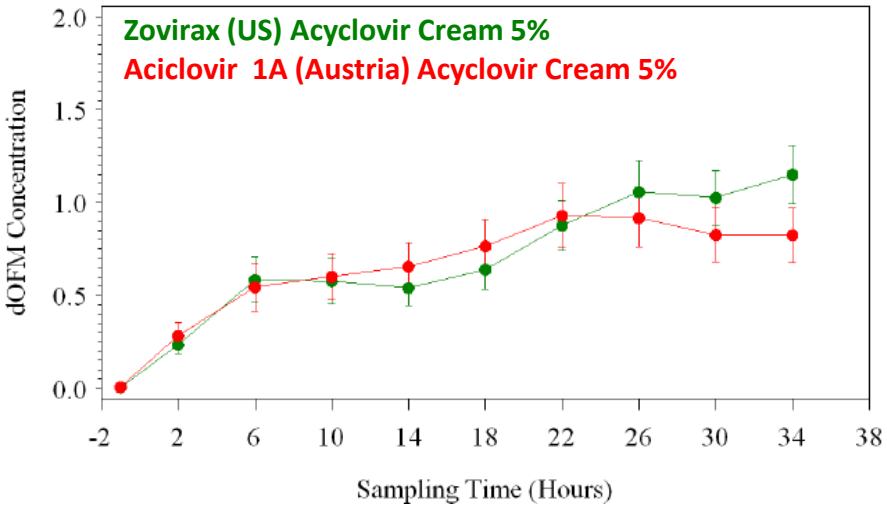
Image courtesy of Joanneum Research



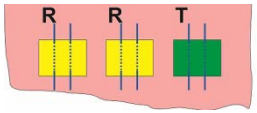
Acyclovir Cream 5% *in vivo* BE

- Dermal Pharmacokinetics by dOFM (20 subjects)





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%]



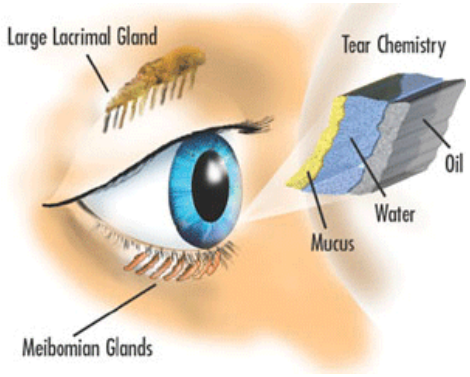
Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]
log(C_{max})	[-0.498 ; 0.022] or [60.8 % ; 102.2%]

JOANNEUM RESEARCH HEALTH

Ophthalmic Products

Ophthalmic Products

- Nine coordinated grants on in vitro characterization, drug release, and drug delivery modeling
  - Modeling and simulation tool chain: PBPK for ophthalmic delivery
  - In vitro release methods
    - University of Eastern Finland (suspension)
    - Texas A&M (emulsion)
    - University of Connecticut (ointments)
- Q3 In vitro approach for Q1 and Q2 formulations
  - Cyclosporine Emulsion (2013)
  - Difluprednate Emulsion (2016)
- Other Guidance
  - 10 ophthalmic suspension guidances
  - Research on study designs for aqueous humor PK
  - Q3 approaches



Orally Inhaled Drug Products

Inhalation Products

- Inhalation Product Research
  - Role of dissolution, particle size and PK studies
  - CFD modeling of deposition
  - Non Q1-Q2 inhalation products
- Leads to Guidance: 15 PSGs for inhalation products available

Orally Inhaled Drug Products: Weight-of-Evidence Approach

2013
1st product-specific guidance for OIDP published

Device and Formulation Design	Comparative In Vitro Studies
Comparative Pharmacokinetic Studies	Comparative Pharmacodynamics or Clinical Endpoint Studies

2016
Generic OIDP applications pending for review

FDA Research Coordination for Inhaled Drugs

Formulation

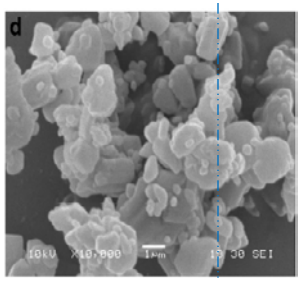
Device

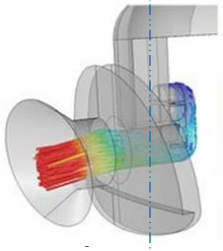
Human Factors

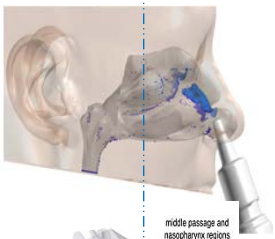
Regional Deposition

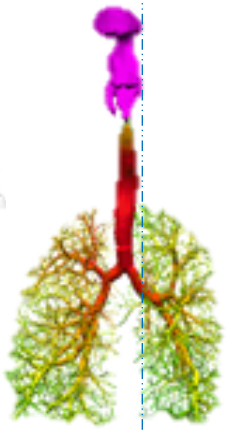
Dissolution

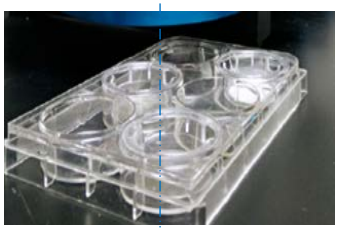
Absorption

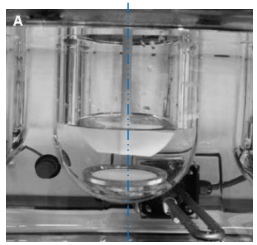


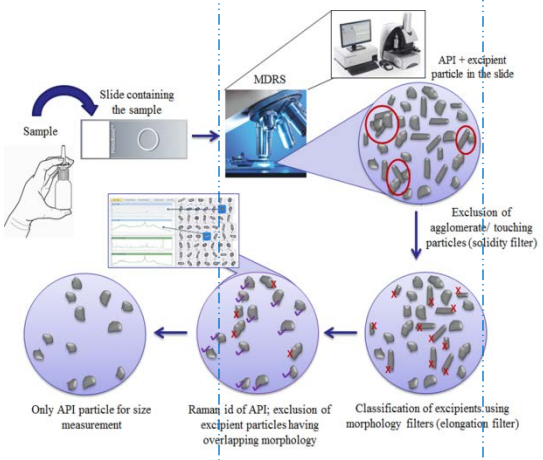


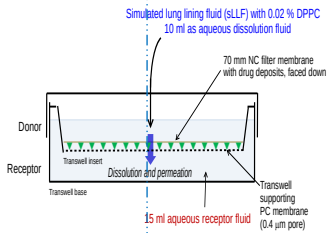












Nasal Products

- Nasal Products
  - Use of PK studies alone for BE: in vitro, in vivo and modeling projects
- Innovative Technology
  - MDRS particle sizing
  - Instrument first available in 2012
  - ANDA approval in 2016 supported by this technology

WRAPPING IT UP

Two Approaches to Locally Acting Equivalence

- Q3 Characterization and Performance
  - Ophthalmic and dermatological focus: sites where application is direct
  - Key guidance on ophthalmic emulsions and topical ointments
  - ANDAs have been approved based on Q3 approaches
  - Does not allow Q1/Q2 differences
- Weight-of-evidence approach
  - Used for nasal and inhalation: sites where there is indirect delivery and delivery device
  - Allows Q1/Q2/Q3 differences
  - PD/Clinical component is challenging for some active ingredients (inhaled corticosteroids)

Stepping Forward: Integration

- Expand Q3/characterization approaches to nasal and inhalation products
- Go beyond Q3
  - Q1/Q2/Q3 approaches limits formulation flexibility and could limit generic competition
  - Non Q1-Q2 products often need an in vivo component of BE
    - PD measures, direct sampling or systemic PK are alternatives to clinical endpoints
    - Modeling and simulation is critical to the interpretation of in vivo data (especially PK) for locally acting products

Discussion Questions

- Please help identify specific gaps in our understanding of locally acting drugs. Discuss how these gaps might be bridged through appropriate research investigations.
- What should we look for in prioritizing research investigations?
- Are there common themes across the locally-acting drugs that might yield useful research targets?

Priorities for the Panel

- Development of alternatives to FEV clinical endpoint BE studies for inhaled corticosteroids
- Development of alternatives to clinical endpoint BE studies for locally-acting nasal products
- Evaluate the impact of identified differences in the user-interface on the substitutability of generic drug-device combination products
- Expansion of characterization based BE methods across the full space of topical dermatological products
- Expansion of characterization based BE methods across the full space of ophthalmic products

Discussion Panel

- Charlie DiLiberti, MS, Montclair Bioequivalence
- Candis Edwards, MS, Amneal
- Guenther Hochhaus, PhD, University of Florida
- Josephine Nguyen, MD, U.S. Navy & USUHS
- John Peters, MD, Deputy Director, OGD
- Badrul Chowdury, MD PhD, Director, DPARP, OND
- Sarah Yim, MD, Director, DCR, OGD
- Markham Luke, MD PhD, Director, DTP, OGD
- Sau (Larry) Lee, PhD, OPS
- Denise Cook, MD, DDDP, OND
- Kimberly Witzmann, MD, ORS, OGD
- Sam Raney, PhD, ORS, OGD

Ears to you!

Acknowledgements

All of my FDA colleagues and staff, current and previous, and their collaborators, including:

- Robert Lionberger, PhD
- Sam Raney, PhD
- Kimberly Witzmann, MD
- Darby Kozak, PhD
- Stephanie Choi, PhD
- Jonathan Wilkin, MD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