AAPS Workshop on

Locally Acting Drug Products: Bioequivalence Challenges and Opportunities

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Alternative Approaches to Demonstrate Bioequivalence of Ophthalmic Products and the Role of Regulatory Science

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FDA U.S. FOOD & DRUG ADMINISTRATION

Evaluation of Generic Ophthalmic Products (under an ANDA – 505(j))

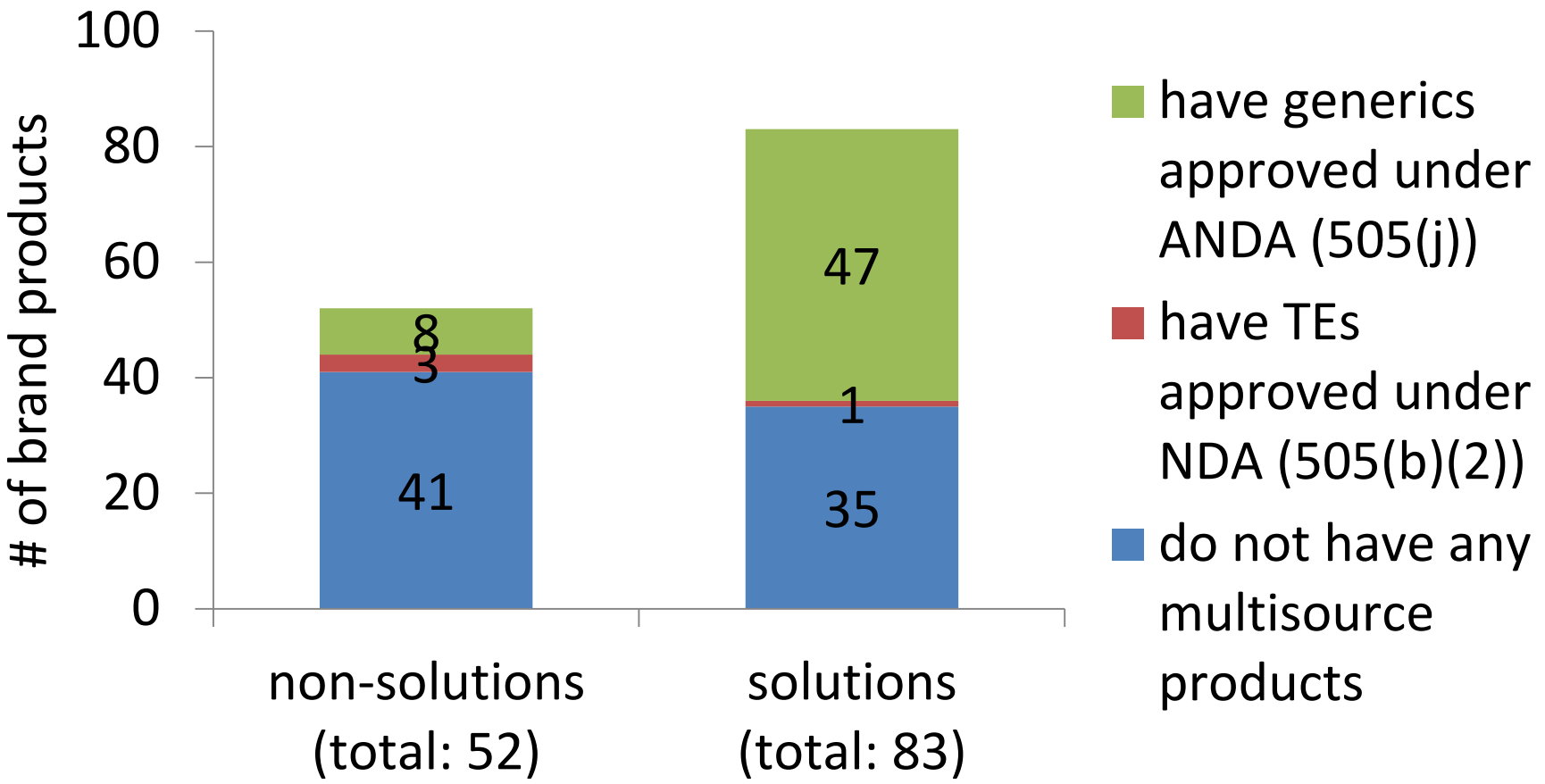
- If the test formulation is Q1/Q2 equivalent to the reference product:
  - Solutions – Bioequivalence is self-evident (waiver of in vivo study under 21 CFR 320.22 (b)(1))
  - Non-solutions – Bioequivalence should be demonstrated by one or more of the following studies:
    - Clinical endpoint study
    - PK study in aqueous humor
    - Microbial kill rate study
    - In vitro studies (Q3 characterization)
- If the test formulation is not Q1/Q2 equivalent to the reference product, a clinical endpoint study must be conducted (for both solutions and non-solution dosage forms)

Ophthalmic solution ANDA submissions

- Over 90% of all ophthalmic ANDA submissions are for solutions
- 85.26% of total ophthalmic solution ANDAs were submitted after January 2008
- Only 28.5% of ANDAs were adequate after the first review cycle
- Most common deficiency (over 90%) related to insufficient comparative physicochemical characterization:
  - Specific gravity
  - pH
  - Osmolality
  - Buffer capacity
  - Tonicity
  - Viscosity
  - Other parameters as deemed appropriate

Please see AAPS poster #03T0430 (Common Deficiencies in ANDAs for Locally Acting Ophthalmic Products with In Vivo Bioequivalence Study Waiver Submissions)

Approved Ophthalmic Brand Drug Products



Approved Ophthalmic Therapeutic Equivalents: Non-Solutions

Active Ingredient	Dosage Form	TE code	Application #	Date Approved
BACITRACIN ZINC; HYDROCORTISONE; NEOMYCIN SULFATE; POLYMYXIN B SULFATE	ointment	AT	A65213	7/25/12
BACITRACIN ZINC; NEOMYCIN SULFATE; POLYMYXIN B SULFATE	ointment	AT	A60764	1/22/81
BACITRACIN ZINC; NEOMYCIN SULFATE; POLYMYXIN B SULFATE	ointment	AT	A65088	2/6/04
BACITRACIN ZINC; POLYMYXIN B SULFATE	ointment	AT	A64028	1/30/95
BACITRACIN ZINC; POLYMYXIN B SULFATE	ointment	AT	A65022	2/27/02
DEXAMETHASONE; NEOMYCIN SULFATE; POLYMYXIN B SULFATE	ointment	AT	A62938	1/31/89
DEXAMETHASONE; NEOMYCIN SULFATE; POLYMYXIN B SULFATE	ointment	AT	A64063	7/25/94
ERYTHROMYCIN	ointment	AT	A64030	7/18/96
ERYTHROMYCIN	ointment	AT	A64067	7/29/94
GENTAMICIN SULFATE	ointment	AT	A65024	7/30/04

Approved Ophthalmic Therapeutic Equivalents: Non-Solutions

Active Ingredient	Dosage Form	TE code	Application #	Date Approved
DEXAMETHASONE; NEOMYCIN SULFATE; POLYMYXIN B SULFATE	Suspension	AT	A64135	9/13/95
DEXAMETHASONE; NEOMYCIN SULFATE; POLYMYXIN B SULFATE	Suspension	AT	A62341	5/22/84
DEXAMETHASONE; TOBRAMYCIN	suspension	AB	A64134	10/27/99
PREDNISOLONE ACETATE	suspension	AB	N17469	7/10/73
TIMOLOL MALEATE	Gel forming solution	AB	N20963	10/21/98

Challenges in Generic Ophthalmic Drug Development and Approval

- Clinical studies require large numbers of subjects due to high intersubject variability
- For products with modest clinical efficacy, clinical studies may not be sensitive enough to detect differences when comparing a potential generic product to the branded product
- Alternative approaches to demonstrate equivalence (other than clinical studies) are warranted to provide a pathway for generic approval of ophthalmic products, such as in vitro studies

Recommended bioequivalence studies for ophthalmic products

- 28 product-specific guidances for ophthalmic products posted since 2008
- 16 product-specific guidances for nonsolution products:
  - Clinical endpoint study – 6
  - PK study in aqueous humor – 8
  - In vitro study - 6

Product-Specific Guidances with In vitro recommendations

- Cyclosporine emulsion (posted Jun 2013; revised Oct 2016)
- Difluprednate emulsion (posted Jan 2016)
- Dexamethasone; tobramycin suspension, 0.05%/0.3% and 0.1%/0.3% (revised Jun 2016)
- Bacitracin ointment (revised Oct 2016)
- Erythromycin ointment (revised Oct 2016)

Cyclosporine emulsion guidance

- Two options: In Vitro or In Vivo (clinical endpoint) Study
- In Vitro option:
  1. Q1/Q2 sameness
  2. Acceptable comparative physicochemical characterization of the Test and RLD
  3. Acceptable comparative in vitro drug release rate from Test and RLD

Please see AAPS poster #03T1130 (Scientific Considerations for Generic Cyclosporine Ophthalmic Emulsion In Vitro Bioequivalence Studies)

In Vitro Studies (Q3 Characterization)

- Even if a product is formulated Q1/Q2, there could be differences in the arrangement of matter within the dosage form which may impact product performance
- These differences in arrangement of matter (structural similarity – “Q3”) arise from differences in manufacturing
- Differences in Q3 can be evaluated by comparative physicochemical data
- Sameness in physicochemical characteristics will ensure equivalence in in vivo performance

In Vitro Studies (Q3 Characterization)

- Recommended characterization data:
  - Globule size distribution (with statistical analysis)
  - Viscosity profile as a function of applied shear
  - pH
  - Zeta potential
  - Osmolality
  - Surface tension
  - Drug distribution in different phases within the formulation

*These characterization studies are specific to this product, and do not apply to other products.

In Vitro Studies (Q3 Characterization)

- Globule size distribution
  - Drug release/clearance
  - Product stability
- Viscosity
  - Ocular retention time (bioavailability)
  - Drug release
- pH
  - Irritation (drug absorption)
  - Stability, solubility, permeability

- Zeta potential
  - Adhesion to cell membranes
  - Product stability
- Osmolality
  - Irritation, tissue damage
  - Permeability
- Surface tension
  - Corneal permeation
  - Irritation
- Drug distribution within different phases
  - bioavailability

Dexamethasone; Tobramycin Ophthalmic Suspension Guidance

- In Vitro Option:
  1. Q1/Q2 sameness
  2. Acceptable comparative physicochemical characterization of the Test and RLD:
     - Crystalline habit
     - Appearance, pH, specific gravity, osmolality, surface tension, buffer capacity, viscosity
     - Re-dispersibility
     - Soluble fraction of dexamethasone in final product
     - Unit dose content (with PBE)
     - Drug particle size distribution (with PBE)
  3. Acceptable comparative in vitro drug release rate from Test and RLD
  4. Acceptable comparative in vitro antimicrobial kill rates from Test and RLD

Erythromycin Ophthalmic Ointment Guidance

1. Q1/Q2 sameness
2. Acceptable comparative physicochemical characterization of the Test and RLD:
   - Solid state form
   - Appearance
   - Acidity and alkalinity of the extracted ointment base
   - Rheological properties
   - Drug particle size distribution
   - In vitro drug release rate

GDUFA Regulatory Science Program

- Supports access to generic drugs in all product categories
  - inhalation, nasal, topical dermatological, ophthalmic, liposomal, sustained release parenteral
- Development of new tools to evaluate drug equivalence and support drug development
  - Simulation tools to predict drug absorption
  - Advanced analytical methods for product characterization
  - In vitro methods to predict in vivo performance

Generic Drug User Fee Amendments (GDUFA)

- Passed in July 2012 to speed access to safe and effective generic drugs to the public
- Requires user fees to supplement costs of reviewing generic drug applications and provide additional resources, including support for regulatory science research
- Largest user fee program to directly support regulatory science research activities

GDUFA Regulatory Science Program

- Implemented by the **Office of Research and Standards** in the Office of Generic Drugs
  - External collaborations: academia, industry
  - Internal collaborations: FDA labs, other government agencies

Ophthalmic Research Program - Objectives

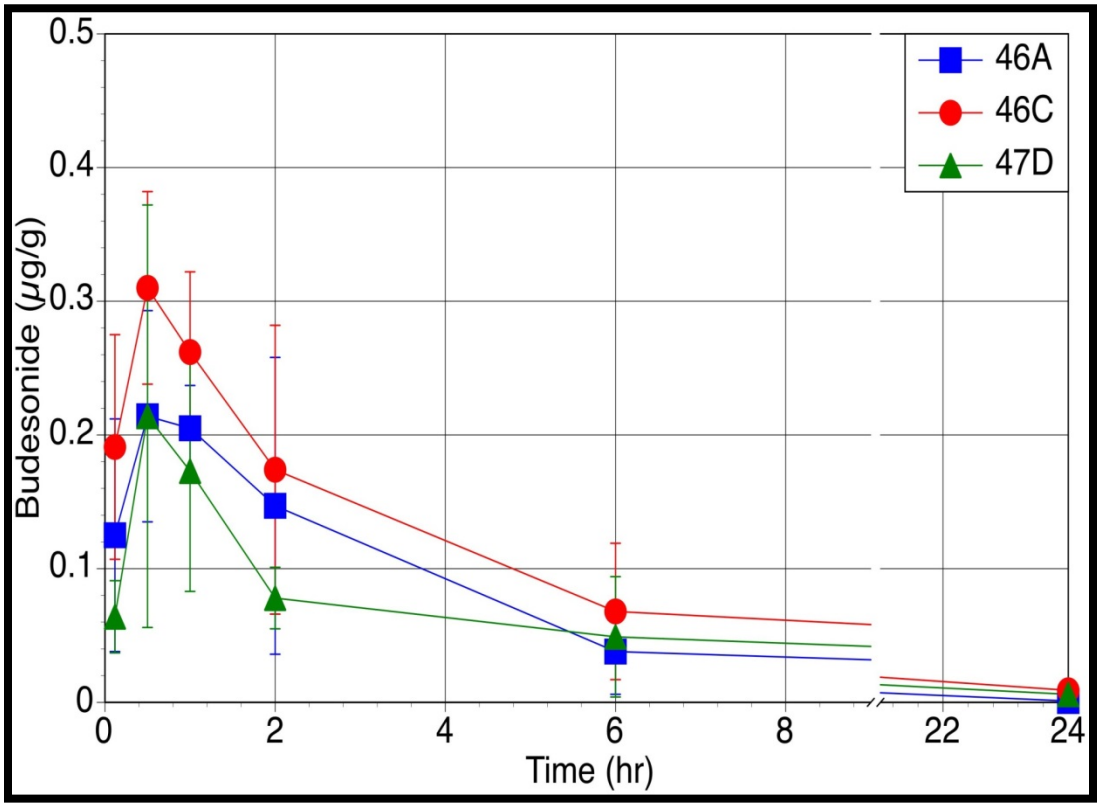
- Investigation of key physicochemical properties that affect drug release and ocular bioavailability
- Development of in vitro release testing methods which are predictive of in vivo release
- In vitro-In vivo correlations
- Physicochemical characterization methods
- Predictive modeling of ocular drug absorption

Effect of physicochemical parameters on ocular bioavailability

- Awarded in 2012 to University of Colorado-Denver
- Three compositionally equivalent budesonide suspensions prepared by different manufacturing methods
- Formulations had different particle size and viscosity

Formulation	Size (nm)	PDI	Viscosity (cPs)	Osmolarity (mOsm)
46A	707	0.24	4.89	284
46C	1980	0.12	53.2	279
47D	1954	0.21	4.92	285

- Conducted PK study in aqueous humor of rabbits
- None of the three suspensions were bioequivalent in aqueous humor PK
- An increase in viscosity appeared to improve the bioavailability of budesonide dosed as micro-suspensions



Bourne D, et al. Effect of Particle Size and Viscosity of Ophthalmic Suspensions on Ocular Bioavailability. ARVO. Denver, CO. June 2015. 5722

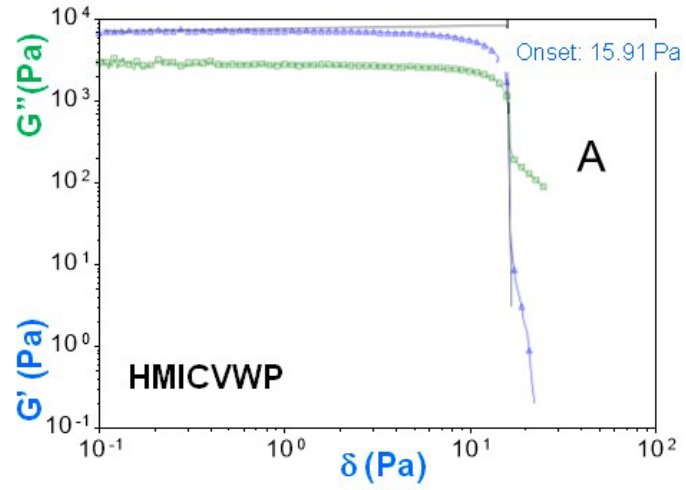
In Vitro-In Vivo Correlations (IVIVC) for ocular implants

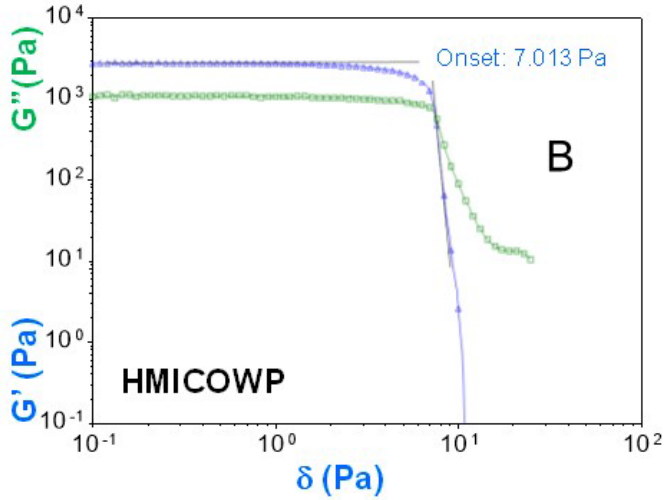
- Objective: to develop an in vitro drug release test which correlates with in vivo ocular absorption. Ocular bioavailability is assessed in an animal model.
- Two awards in 2013:
  - Auritec Pharmaceuticals
  - University of Colorado-Denver: dexamethasone intravitreal implant
    - Preparation of compositionally equivalent dexamethasone implants
    - Degradation of dexamethasone after release from implants

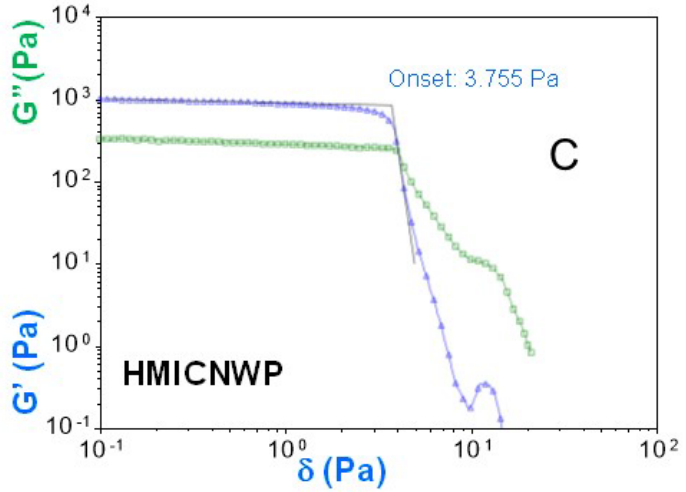
In Vitro Release Testing (IVRT)

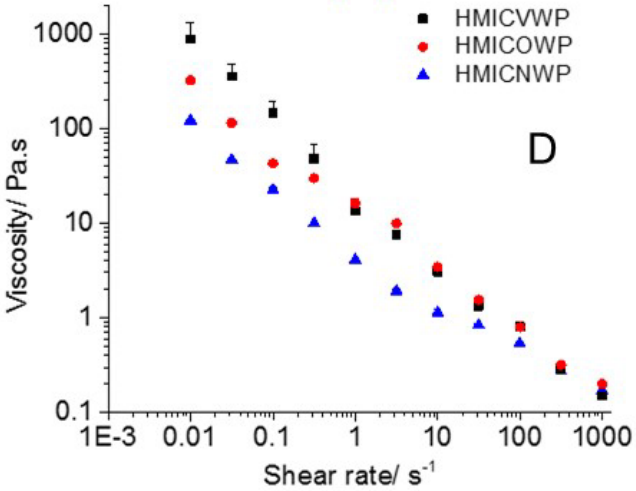
- Objective: to develop biorelevant in vitro drug release assays for ocular dosage forms. The release method should be able to discriminate compositionally equivalent formulations with manufacturing differences
- Multiple awards in 2014:
  - Suspensions (Univ of Finland)
    - Physical Formulation Features and Ocular Absorption from Topical Suspensions: Toward Mechanistic Understanding (05T0430)
  - Emulsions (Texas A&M)
    - Towards Development of Bioequivalence Testing Method for Topical Ophthalmic Emulsion of Difluprednate (10T0130)
  - Ointments (Univ of Connecticut – 2 investigators)
    - Manufacturing Differences on Physicochemical and *In Vitro* Release Characteristics of Semisolid Ophthalmic Ointments (23M0930)
    - Impact of Excipient Sources on *In Vitro* Drug Release Characteristics of Semisolid Ophthalmic Ointments (34T0900)
  - Intravitreal systems (Univ of California San Diego)

Rheological profiles of ointments manufactured with different petrolatum sources

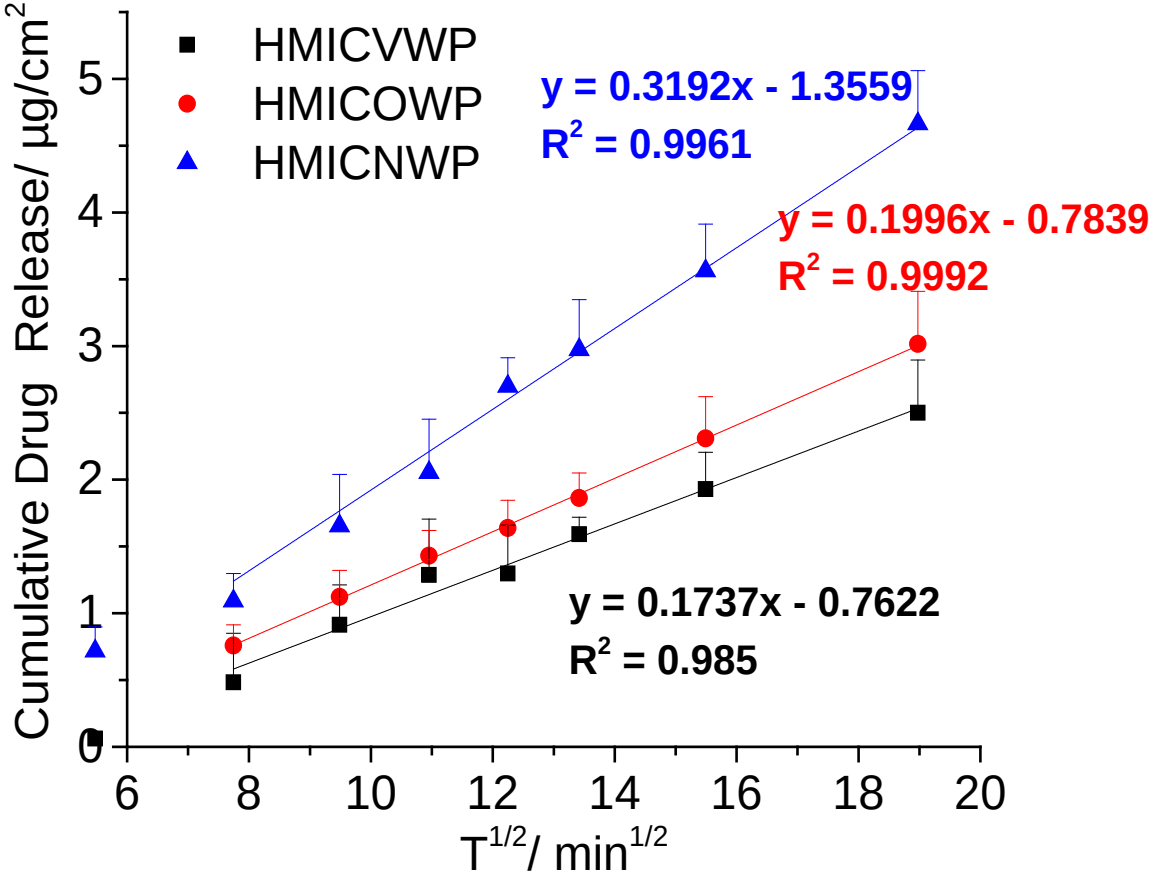








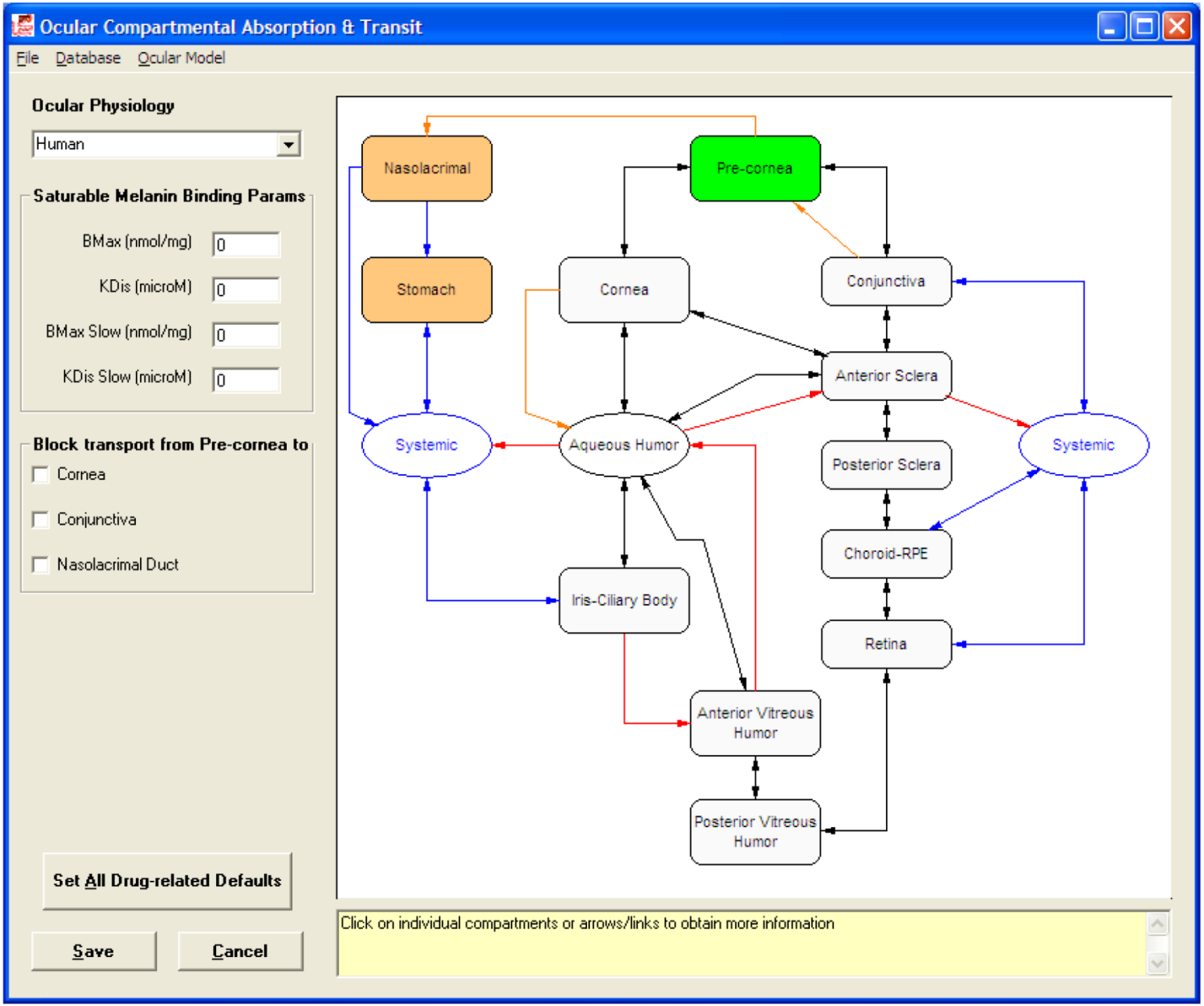
In vitro drug release profiles of ointments manufactured with different petrolatum sources



Please see AAPS poster #34T0900 (Impact of Excipient Sources on *In Vitro* Drug Release Characteristics of Semisolid Ophthalmic Ointments)

Predictive modeling of ocular absorption

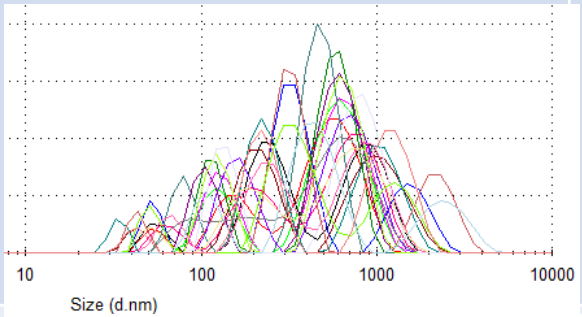
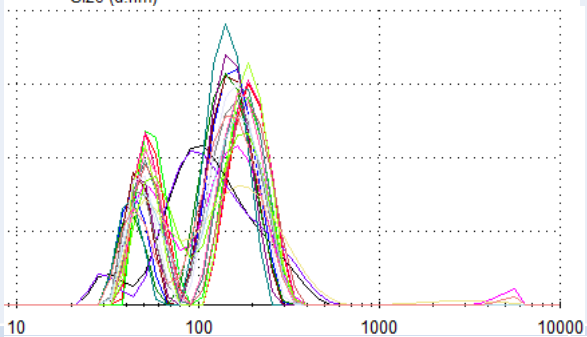
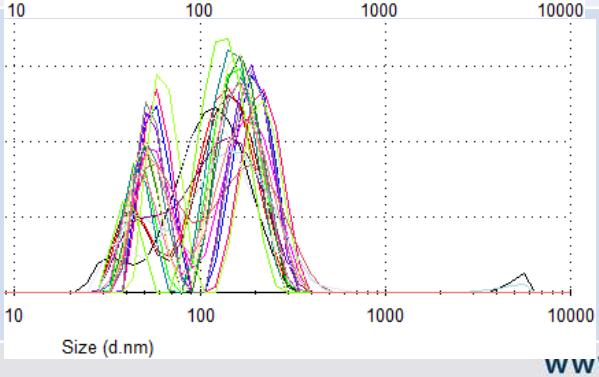
- Objective: To develop, evaluate and improve physiologically based ophthalmic absorption and pharmacokinetic models
- Two awards in 2014: (3-year projects)
  - Improve Ocular Compartmental Absorption and Transit Model - Simulations Plus
  - 2D/3D Ocular finite element model with PBPK - CFD Corp


Ocular Compartmental Absorption & Transit
File
Database
Ocular Model
Ocular Physiology
Human
Saturable Melanin Binding Params
BMax (nmol/mg)
0
KDis (microM)
0
BMax Slow (nmol/mg)
0
KDis Slow (microM)
0
Block transport from Pre-cornea to
Cornea
Conjunctiva
Nasolacrimal Duct
Set All Drug-related Defaults
Save
Cancel
Nasolacrimal
Pre-cornea
Stomach
Cornea
Conjunctiva
Anterior Sclera
Systemic
Aqueous Humor
Posterior Sclera
Systemic
Choroid-RPE
Iris-Ciliary Body
Retina
Anterior Vitreous Humor
Posterior Vitreous Humor
Click on individual compartments or arrows/links to obtain more information

Physicochemical characterization methods

- Objective: to develop and evaluate test methods to properly evaluate physicochemical characteristics of ophthalmic formulations
- Internal studies by FDA labs: Nanocore facility (CDRH), Division of Product Quality Research (CDER)
  - Globule size measurement of nanoemulsions
  - Rheology
  - In vitro release
  - Determination of drug distribution in multi-phase formulations
  - Manufacture of test formulations

Restasis® Measured by Dynamic Light Scattering

Dilution Factor	Histogram (Intensity, % vs. Size, nm)	Z-Average (d. nm) 0.89 cP viscosity	PdI	Intensity Peaks (d. nm, % Intensity)
1X Stock		301.2 ± 11.4	0.56 ± 0.03	877.6 (52%) 260.5 (39%) 67.1 (9%)
10X		103.7 ± 0.9	0.28 ± 0.01	180.0 (67%) 53.6 (33%)
100X		101.2 ± 1.3	0.27 ± 0.01	149.7 (78%) 46.3 (22%)

New FY16 Award

- Pulsatile microdialysis for in vitro release of ophthalmic emulsions (Physical Pharmaceutica LLC)
- Aims to develop an in vitro drug release testing method using pulsatile microdialysis and to evaluate its application for ophthalmic emulsions
- Expected outcomes: report a sensitive drug release method for ophthalmic emulsions and understand the drug release mechanism and critical parameters that may affect the release profile from emulsions to help review of ANDAs and guidance development

Regulatory Impact

- FDA product-specific guidances
- Review of regulatory submissions (ANDAs, pre-ANDA meeting requests, Controlled Correspondences)
- Presentations at scientific conferences
- Manuscripts in progress

FY15 Regulatory Science Research Report

- A report of FY15 regulatory science research activities conducted under GDUFA is publicly available
- Sub-section on Ophthalmic Products:
  - Project titles and collaborators
  - Publications and presentations
  - Outcomes
- FY16 Report to be published later this year

http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm500571.htm

Summary

- Alternative approaches to demonstrate bioequivalence of generic ophthalmic non-solution products are warranted
- Scientific research is needed to support development of new approaches for bioequivalence
- OGD implements the Regulatory Science Research Program under GDUFA to:
  - Further the understanding of in vitro and in vivo performance of ophthalmic drug products
  - Support development of new approaches to evaluate equivalence of generic ophthalmic products

Questions

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GDUFA Regulatory Science Website:
www.fda.gov/GDUFARegScience

References

- Clinical, Pharmacokinetic, and *In Vitro* Studies to Support Bioequivalence of Ophthalmic Drug Products. *AAPS J*, 2016, *18* (4), pp 1032-8.
- Product-Specific Recommendations for Generic Drug Development http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm