An Update on FDA's Research Program for Ophthalmic Generic Products

Stephanie H. Choi, Ph.D.
Office of Research and Standards
Office of Generic Drugs
US Food and Drug Administration

2016 CRS Annual Meeting (Seattle, WA)

Outline

- Overview of the GDUFA Regulatory Science Program
- Ophthalmic research areas:
  - Effect of physicochemical parameters on ocular bioavailability
  - In Vitro-In Vivo Correlations (IVIVC)
  - In Vitro Release Testing (IVRT)
  - Physicochemical characterization methods
  - Predictive modeling of ocular drug absorption

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

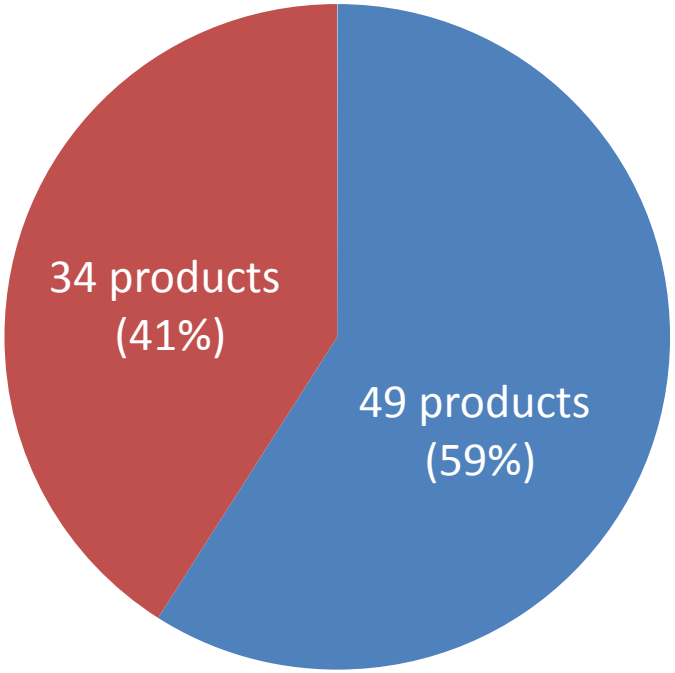
- Supports access to generic drugs in all product categories
  - inhalation, nasal, topical dermatological, ophthalmic, liposomal, sustained release parenteral
- Development of new tools to evaluate drug equivalence and support drug development
  - Simulation tools to predict drug absorption
  - Advanced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

GDUFA Regulatory Science Program

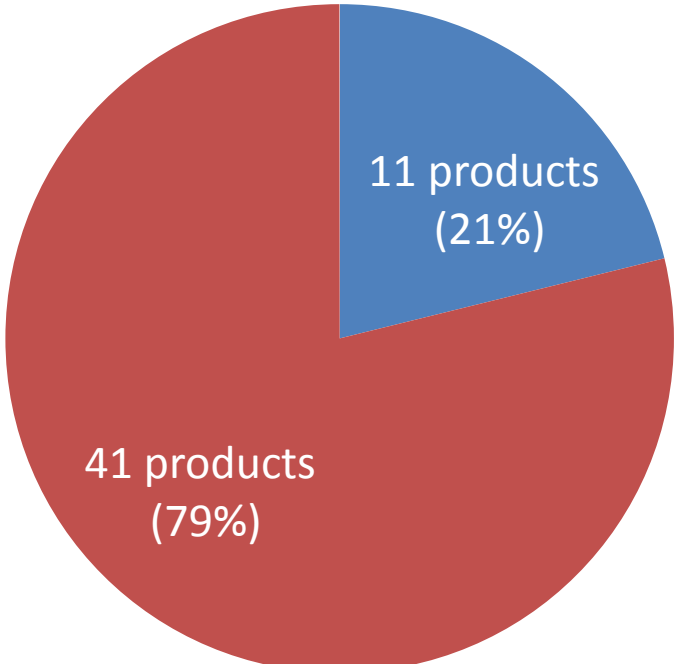
- Implemented by the **Office of Research and Standards** in the Office of Generic Drugs
  - External collaborations: academia, industry
  - Internal collaborations: FDA labs, other government agencies

Approved Ophthalmic Drug Products

solutions (total: 83)



non-solutions (total: 52)



- Multisource products available
- Not available

Evaluation of Generic Ophthalmic Products

- Solutions – No clinical or comparative in vitro studies required (if the generic has the same composition as the brand)
- Non-solutions – One or more of the following studies are required:
  - Clinical endpoint study
  - Clinical pharmacokinetic aqueous humor study
  - In vitro microbial kill rate study
  - In vitro characterization and release studies

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

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

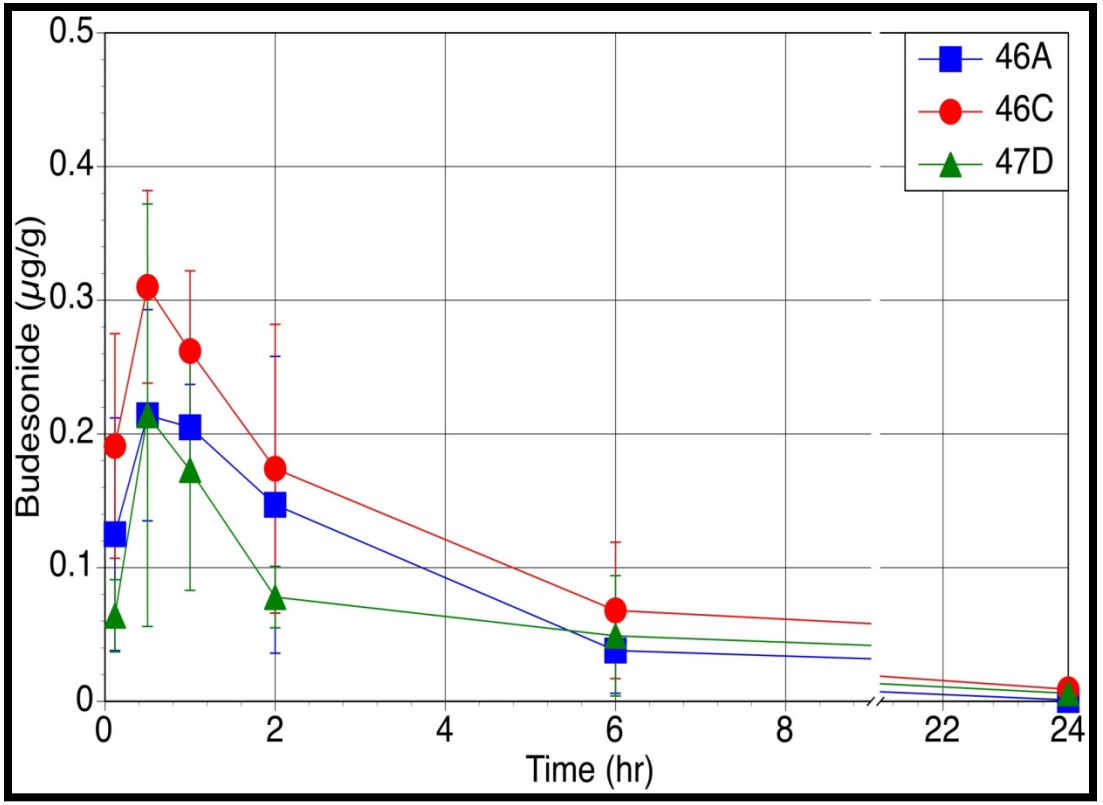
Effect of physicochemical parameters on ocular bioavailability [1]

- 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

Effect of physicochemical parameters on ocular bioavailability [1]

- 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



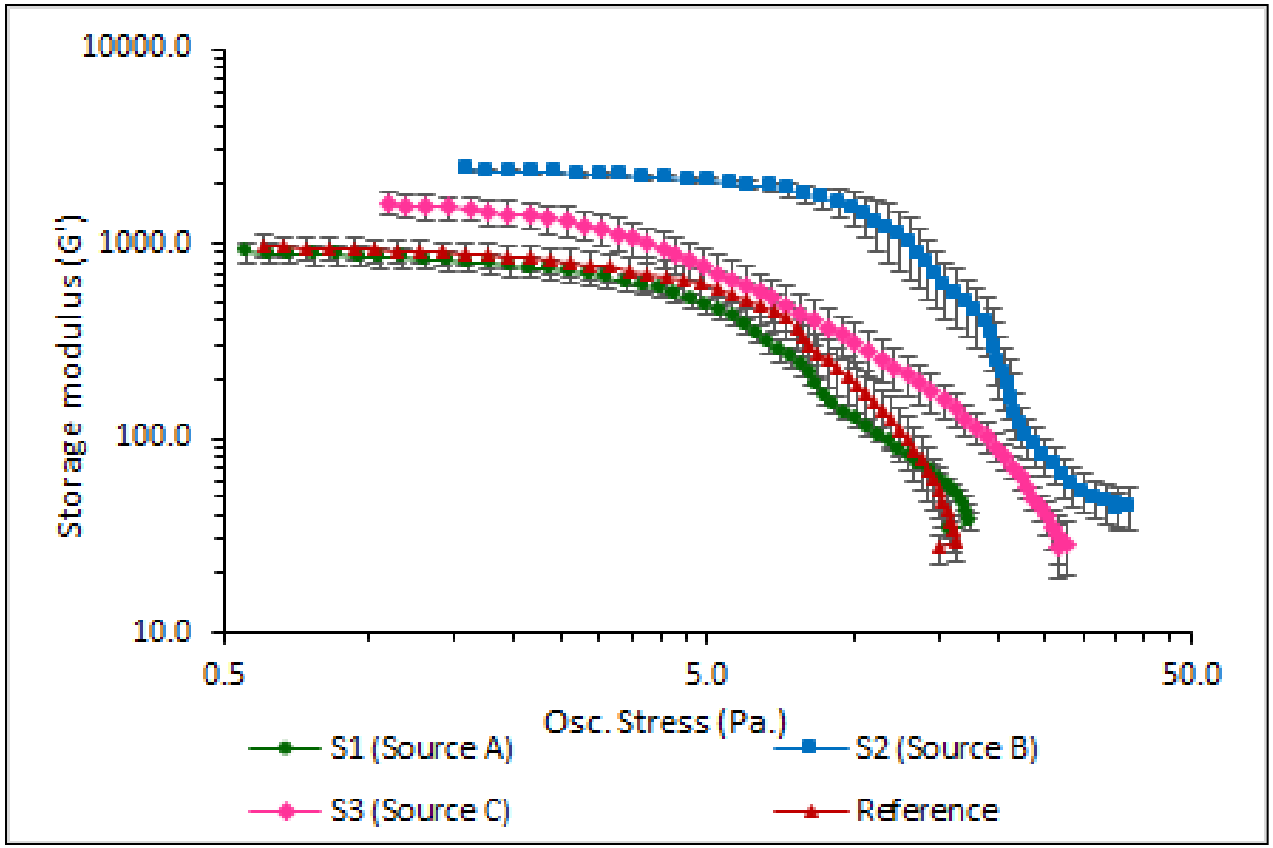
In Vitro-In Vivo Correlations (IVIVC) for ocular implants

- 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 [2]
    - Degradation of dexamethasone after release from implants [6]

In Vitro Release Testing (IVRT)

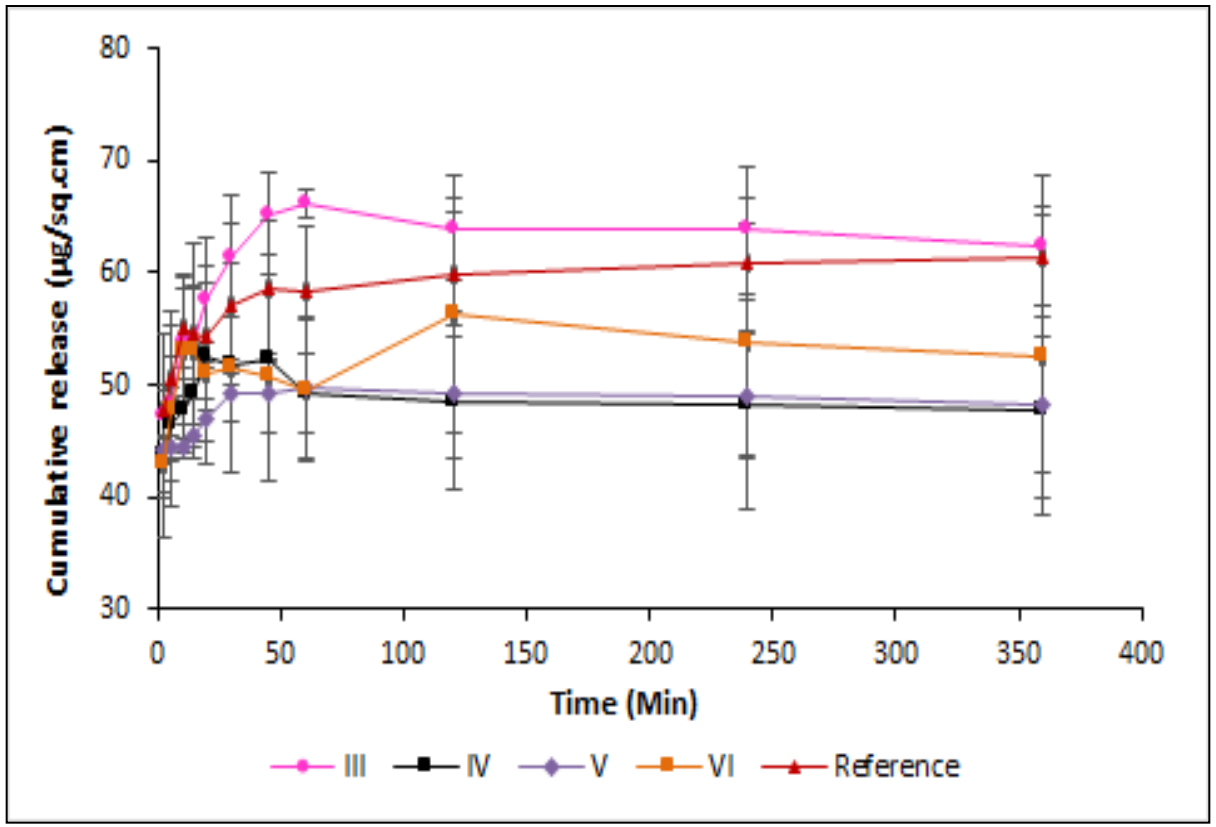
- Objective: to develop biorelevant in vitro drug release assays for ocular dosage forms. The release method should be able to discriminate compositionally equivalent formulations with manufacturing differences
- Multiple awards in 2014:
  - Suspensions (Univ of Finland)
  - Emulsions (Texas A&M) [3]
  - Ointments (Univ of Connecticut – 2 investigators) [5]
  - Intravitreal systems (Univ of California San Diego)

Characterization of semisolid formulations [6]



Petrolatum source significantly influenced the rheology of the manufactured ointment formulations

IVRT of semisolid formulations [6]



Drug release using USP apparatus IV shows differences in release among formulations with equivalent composition but differences in manufacturing process

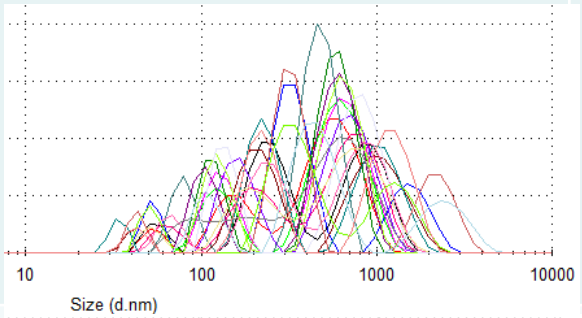
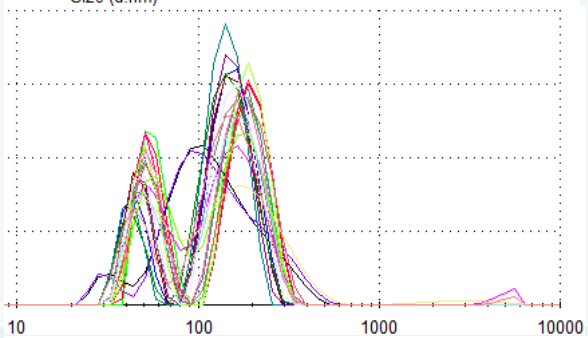
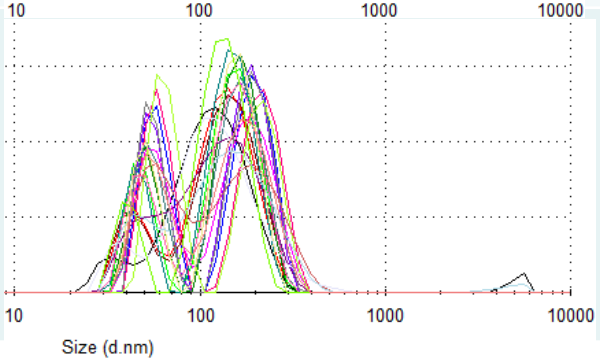
Physicochemical characterization methods

- 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 [4]
  - Rheology
  - In vitro release
  - Determination of drug distribution in multi-phase formulations
  - Manufacture of test formulations

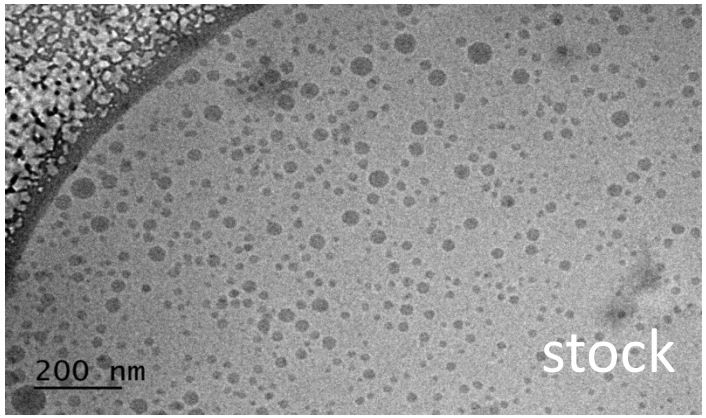
Globule size measurement of Restasis®

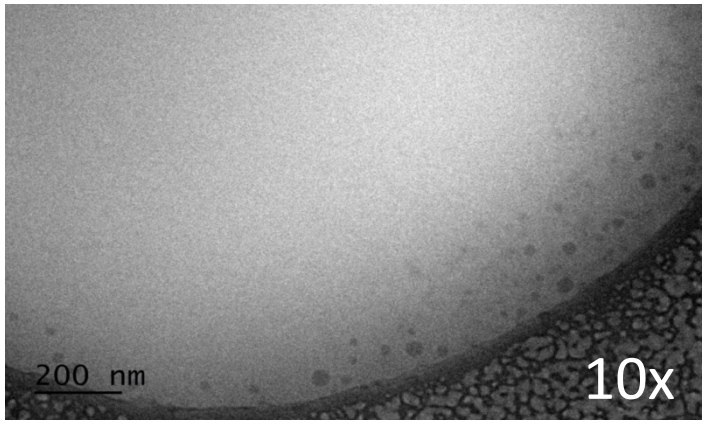
- The globule size distribution of Restasis (cyclosporine ophthalmic emulsion) was measured using TEM and DLS to investigate a suitable method for measurement

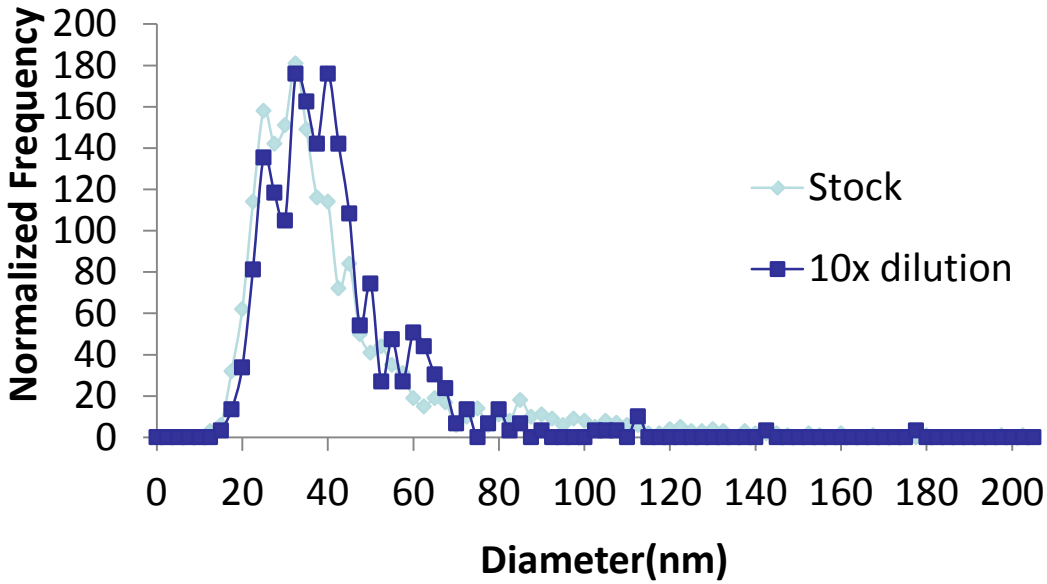
Restasis® Measured by Dynamic Light Scattering

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%)

Cryo - Transmission Electron Microscopy of Restasis®







	Number-averaged Size	Max Size	Min Size
Restasis stock	38.9 ± 22.4 nm	202.2 nm	11.0 nm
Restasis 10 X dilution	39.6 ± 16.6 nm	177.2 nm	15.0 nm

- Restasis stock and 10X dilution had similar number-averaged sizes, 38.9 and 39.6 nm, respectively
  - No evidence of large emulsion globules or dilution effect.

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 [7]
  - 2D/3D Ocular finite element model with PBPK - CFD Corp

Regulatory Impact

- FDA product-specific guidances:
  - Cyclosporine ophthalmic emulsion (revised February 2016)
  - Difluprednate ophthalmic emulsion (new February 2016)
  - Dexamethasone; Tobramycin ophthalmic suspension (revised June 2016)
- 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 has been posted:
  - Project titles and collaborators
  - Publications and presentations
  - Outcomes

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

Summary

- FDA has an extensive ophthalmic research program established under GDUFA covering a wide range of dosage forms (suspensions, emulsions, ointments, implants)
- The research program is implemented through collaborations with external and internal investigators
- Results of the research studies are used 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

Acknowledgments

- Abir Absar, Ph.D.
- Jianghong Fan, Ph.D.
- Robert Lionberger, Ph.D.
- Bryan Newman, Ph.D.
- Peter Petrochenko, Ph.D.
- Yan Wang, Ph.D.
- Sook Wong, B.S.
- Jiwen Zheng, Ph.D.

References

1. Bourne D, Vooturi S, Panda J, Choi S, Kim H, Yandrapu S, et al. Effect of Particle Size and Viscosity of Ophthalmic Suspensions on Ocular Bioavailability. Association for Research in Vision and Ophthalmology. Denver, CO. June 2015. 5722
2. Bai Y, Bourne D, Wang Y, Choi S, Kompella UB. Sustained Release Dexamethasone Implants for In Vitro – In Vivo Correlations. Association for Research in Vision and Ophthalmology. Denver, CO. 2015. 4154.
3. Palakurthi S, Cai D, Qiu J, Absar M, Choi S. Preparation and Evaluation of Difluprednate Topical Ocular Emulsions. American Association of Pharmaceutical Scientists. Orlando, FL. 2015. M1271
4. Peter E. Petrochenko, Mohammad S. Absar, Yong Wu, Sook Y. Wong, Stephanie Choi, Jiwen Zheng. Characterization of the globule size distribution of Cyclosporine ophthalmic emulsion to establish bioequivalence of a Test formulation. American Association of Pharmaceutical Scientists. Orlando, FL. 2015. T3350

References

5. Shilpa Patere, Khaetthareeya Sutthanut, Bryan Newman, Stephanie Choi, Michael Jay and Xiuling Lu. Influence of Excipients on Physicochemical Characteristics of Ocular Semisolid Formulations and Their In Vitro Drug Release. American Association of Pharmaceutical Scientists. Orlando, FL. 2015. W5057
6. Brock Matter, Alireza Ghaffari, David Bourne, Yan Wang, Stephanie Choi, and Uday Kompella. Dexamethasone Degradation During In Vitro Release from an Intravitreal Implant. Association for Research in Vision and Ophthalmology. Seattle, WA. 2016.
7. Michael B. Bolger, Jessica Spires, James M. Mullin, Joyce Macwan, Jayeeta Ghosh, and Viera Lukacova. Fluorometholone Ocular Suspension PBPK simulations using the OCAT™ model in GastroPlus ™. GTBio, San Diego, March 2015.