December 5, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852


Dear Sir or Madam:

Allergan hereby addresses the Food and Drug Administration’s (FDA) most recent revised Draft Guidance on Cyclosporine, published on October 5, 2016 (the “October 2016 Draft Guidance”).1 The agency’s continuing, significant revision of the in vitro analyses that it might recommend for evaluating the bioequivalence of a proposed generic to RESTASIS® (cyclosporine ophthalmic emulsion, 0.05%) reflects the continuing absence of agreed methods that have been validated as a proxy for in vivo bioavailability.

FDA still has not addressed the basic problem with relying on in vitro analyses to establish bioequivalence to RESTASIS, which is that to date no in vitro analyses for this complex product have been validated as a proxy for in vivo bioavailability. Although we continue to believe FDA’s proposed in vitro standards are currently inadequate to satisfy the bioequivalence requirement, we nevertheless submit the following comments with respect to the October 2016 Draft Guidance.

1. **Concerns With Newly Proposed Methodology for Globule Size/Drug Distribution Analysis**

The October 2016 Draft Guidance made some positive, but other negative, changes to the February 2016 Draft Guidance with respect to analysis of drug distribution within cyclosporine ophthalmic emulsion.

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Unjustified Elimination of Requirement for Complementary Analytical Methods: All knowledgeable parties have agreed that the manner in which cyclosporine is distributed across the phases of cyclosporine ophthalmic emulsion may affect the drug’s ocular bioavailability. Allergan also has supplied evidence that different analytical methods and instruments, instrument settings, measurement conditions, and sampling techniques can yield differing results for the same product (e.g., certain methods can better detect large globules, whereas other methods better detect small globules). For example, at least one of nine test emulsions presented by Allergan that appeared similar to RESTASIS using a particle characterization method was shown to be different using a different characterization sizing method. FDA representative Stephanie Choi, Ph.D. reinforced the potentially significant impact of methodological differences in a November 2016 presentation. To address applicable limitations of available methods, FDA’s February 2016 version of the draft guidance included a requirement for “complementary size characterization methods” and also included a variety of additional evaluations related to globule size measurement (e.g., recommending data on undiluted and diluted samples, full profiles and raw data, for all samples tested; information on the instrument, analysis mode (if applicable), dilution medium, and level of dilution used for globule size measurement). In the October 2016 revision, however, FDA removed many of these requirements (complementary methods, full profiles, raw data, etc.). Complementary methods must be employed to perform an accurate and fair evaluation of individual emulsions.

The February 2016 Draft Guidance recommended the use of complementary globule size analytical methods, readily acknowledging that “more than one size characterization method may be necessary to accurately detect the entire globule size distribution.” Surprisingly, however, and without explanation, this requirement has been removed from the October 2016 Draft Guidance. It is essential to bring back the requirement of independent and complementary globule size analytical methods to ensure that the entire globule size range and drug distribution are characterized adequately. Any less rigorous standard is unjustified and unsupportable.

Inadequate Criteria for Scientific Analyses: FDA has not set forth standards to ensure that adequate data would be developed and submitted in specific analyses. Among other issues, the October 2016

2 FDA Joint Response to Citizen Petitions of Allergan, Inc. and of Physical Pharmaceutica, LLC, Docket No. FDA-2015-P-0065-0027 (Feb. 16, 2016) ("2016 FDA Resp.") at 31. See also Choi, S. and Lionberger, R., Clinical, Pharmacokinetic, and In Vitro Studies to Support Bioequivalence of Ophthalmic Drug Products, The AAPS Journal, Vol. 18, No. 4, July 2016: pp 1032-1038 (DOI: 10.1208/s12248-016-9932-z) ("Globule size distribution can change drug release and clearance as globules which are larger in size have a different drug release rate than those which are smaller in size. The clearance rate may also be different for differently sized globules.").

3 See Choi, S., Alternative Approaches to Demonstrate Bioequivalence of Ophthalmic Products and the Role of Regulatory Science, AAPS Workshop on Locally Acting Drug Products: Bioequivalence Challenges and Opportunities (Nov. 12-13, 2016; copy attached) (e.g., Slide 30 shows very different results related to varying dilution factors).

4 Both intensity-weighted and volume-weighted particles should be considered, and PBE evaluations based on D50 and SPAN should be applied to each method used.
Draft Guidance acknowledges that the conventional population bioequivalence (PBE) analysis (based only on D50 and SPAN) is not sufficient to demonstrate bioequivalence. It describes a preference for using statistical metrics to assess differences in globule size distributions of a proposed generic equivalent to RESTASIS, and suggests use of the “earth mover’s distance” (EMD) method for this purpose. In certain aspects, this is a more rigorous approach to comparing globule size distributions of test emulsions versus the reference product; however, there remain important gaps:

- **Number of Samples.** In guidance documents related to other emulsion products, FDA has specified a minimum number of datasets that must be generated to account for variability and to ensure suitable power for analysis. For example, the draft guidance related to difluprednate ophthalmic emulsion states: “The applicants should provide no less than 10 datasets from 3 batches each of the Test and Reference products to be used in the PBE analysis.” Similar minimum specifications are necessary for a cyclosporine ophthalmic emulsion guidance to ensure that proposed generic sponsors rigorously demonstrate sameness of their test products to the reference product. Currently, the October 2016 Draft Guidance provides no minimum number of samples or replicates to accurately characterize each product batch tested.

- **Data Grouping and Distance.** The EMD method is very sensitive to data grouping, group distance, and number of samples and replicates evaluated, yet no guidance has been provided for these critical attributes. By minimally narrowing or broadening the grouping parameters, Allergan’s biostatisticians were able to conclude that a product that originally failed the EMD assessment subsequently passed, and a product that originally passed the EMD assessment subsequently failed. Minimum requirements (such as the minimum number of sizing groups and maximum width of each group into which data may be classified) should be provided to ensure that any discriminatory power of this method is not compromised.

Furthermore, to our knowledge that is the first time the EMD test is being suggested for purposes of evaluating bioequivalence, and FDA has cited no validated relationship to in vitro or in vivo properties of cyclosporine ophthalmic emulsion.

2. **Unaddressed Concerns About Other Analytical Gaps**

FDA has not addressed specific deficiencies that Allergan previously identified during the comment period on the February 2016 Draft Guidance. These issues and concerns carry forward for the October 2016 Draft Guidance. Therefore, Allergan renews its request that FDA address the following issues.

**Changes to Key Manufacturing Components and Processes:** The October 2016 Draft Guidance includes the restriction that “No changes (source, grade, etc.) should be made to the structure forming excipient or solubilizing excipient in the product for commercial batches unless adequate supporting data and risk assessment are provided to demonstrate that the changes will not affect the product performance and
quality." This requirement acknowledges the fundamental importance of source and grade of excipients in RESTASIS, in addition to the Q1/Q2 requirement. 5

The October 2016 Draft Guidance further states that exhibit lots should be at least 1/10th the size of an intended commercial batch, and the manufacturing process and exhibit lots should reflect the process to be used for commercial batches. Allergan previously acknowledged that it is common industry practice to make exhibit batches at 1/10th the size of planned commercial lot scale. However, given the complexity and potential variability of emulsions (which is known to occur during scale-up), FDA should require ANDA applicants to submit detailed process and analytical information demonstrating that smaller exhibit lots are representative of scaled-up, proposed commercial processes.

**In Vitro Release Method:** FDA has acknowledged that none of the common methods known or proposed in the literature for testing in vitro drug release for disperse systems is a good fit for cyclosporine ophthalmic emulsion, and that the burden is on ANDA applicants to develop a suitable in vitro method for measuring drug release. 6 Allergan agrees.

The October 2016 Draft Guidance includes an obligation that any in vitro release methodology should discriminate the effect of production process variability on the test formulation. However, simply including consideration of the effect of process variability on drug release is not sufficient to demonstrate equivalence and interchangeability of a proposed generic emulsion with RESTASIS. The ability of an in vitro release method to discriminate the effects of process variability is quite important for developing a suitable in vitro release method for comparing a proposed generic product with the reference listed drug. However, the October 2016 Draft Guidance seemingly contains a loophole: To discriminate the effect of process variability on drug release, an ANDA applicant could simply select two extreme cases of processing parameters; for example, one with homogenization and one without homogenization (or with very little homogenization). These different processes will produce emulsions with globule sizes differing by several orders of magnitude, and many in vitro release methods could “discriminate” those extreme types of “process variability.” An acceptable in vitro drug release method, however, must be able to discriminate emulsions with more subtle differences that may be observed during development and validation of emulsions. To close the loophole in the October 2016 Draft Guidance, more specific criteria should be identified, such as the following:

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5 Allergan has submitted data to FDA demonstrating that certain excipient differences affect both in vitro and in vivo performance of RESTASIS and slightly altered formulations.

6 FDA Response to Allergan Citizen Petition, Docket No. FDA-2014-P-0304-0042 (Nov. 20, 2014) (“2014 FDA Resp.”) at 25. See also 2016 FDA Resp. at 30 (“[T]he fact remains that a drug’s release rate is a ‘critical determinant’ of bioavailability. ... The current lack of a validated in vitro drug release rate test for ophthalmic emulsions undeniably presents a significant scientific challenge for ANDA Applicants.”).
• The in vitro method should be able to discriminate the effect of globule size distribution variability on drug release from an emulsion: The correlation of globule size distribution and release rate for different emulsions should be demonstrated as a part of in vitro method development and validation. FDA acknowledged that different size globules are expected to show different drug release rates.\textsuperscript{7} Due to current limitations of globule size analytical methods (which are indirect and also can be influenced by method- and instrument-related differences),\textsuperscript{8} it is possible that emulsions with differences in the globule size populations might nevertheless meet the criteria defined in the October 2016 Draft Guidance. In this case, an in vitro release method capable of detecting the impact of subtle particle size differences on release rate would be necessary for distinguishing these emulsions from RESTASIS.

• The in vitro method should be able to discriminate the effect of differences in drug distribution in the various emulsion phases: As a part of method development and validation, the in vitro method should demonstrate that it is capable of detecting differences in the drug content in different phases. Allergan has provided data to FDA showing this distribution can significantly impact in vivo delivery to the tissue site(s) of action.\textsuperscript{9}

• The in vitro method should address the short duration of the dose on the ocular surface: In vitro release methods that involve long duration (hours to days) of drug release are not relevant to drug release on the topical ocular surface, which has very short duration (measured in minutes at most).

• The in vitro method should be capable of separating and measuring release of “free drug” from excipients of the product such as castor oil and polysorbate 80: This should be demonstrated as a part of method development and validation.

• As a part of in vitro release method development and validation, the data need to demonstrate that any membrane selected for drug release measurement is not the rate-limiting barrier. If the membrane were to affect the rate of drug measurement, the test would not accurately reflect a formulation’s actual drug release profile.\textsuperscript{10}

\textsuperscript{7} 2014 FDA Resp. at 14 ("Large globules have a different drug release rate than smaller globules, and the clearance rate may be different for differently sized globules. These factors can be important to bioavailability. Globule size can also affect the emulsion’s stability.")

\textsuperscript{8} 2016 FDA Resp. at 32-34.


\textsuperscript{10} See, e.g., Palakurthi S. et al, Preparation and Evaluation of Difluprednate Topical Emulsions (FDA-sponsored research), Poster Presentation at the 2015 Annual Meeting and Exposition of the American Association of Pharmaceutical Scientists (copy of abstract attached), in which it was shown that the membrane was the rate-limiting barrier. The abstracted Results state: “Mean droplet size of Durezol® was found to be 137.8±2.8 nm. We
Drug distribution in different phases of the emulsion: FDA “agree[s] that how cyclosporine is distributed across the emulsion’s phases may affect the drug’s ocular bioavailability,”\(^{11}\) and we strongly support the statement in the October 2016 Draft Guidance that an ANDA sponsor should “submit information on the drug distribution in different phases within the formulation in addition to the six previously identified physicochemical properties.” This evaluation is meant to address the fact that, as drug distributes to different phases in the emulsion, the kinetic relationship that governs drug partitioning into the ocular tissues of patients will change.

ANDA sponsors must develop and validate techniques to accurately separate and measure drug in different phases of their emulsion (without the test method impacting the analytical result). We request clarification on methodology for conducting this testing and how the data would be used to compare to the RLD. It currently is not evident how FDA will evaluate the sameness of drug distribution profile, which is a prerequisite to ensure bioequivalent levels of drug in the relevant ocular tissues.

There are no stated ranges for other analytical parameters: For all parameters other than globule size, no specificity is provided on how close the test product and RLD need to be to one another. The guidance states that these parameters do not require PBE analysis, for example. We request that FDA clarify the acceptable ranges of these values in comparison with RESTASIS. At a minimum, statistical analysis and comparison of RLD and test emulsions should be conducted.

Evaluation of multiple product lots and replicates: Allergan supports FDA’s stated expectation that ANDA developers will compare physicochemical characteristics across at least three exhibit batches of both test and reference listed drug products. We request that FDA clarify these exhibit batches must be from independent production runs (and may not be sub-batches within a common manufacturing run). We also request that FDA reinforce the obligation of ANDA developers to submit all reports of comparative analyses conducted on the same drug product formulation,\(^{12}\) to ensure a complete and accurate picture of product characteristics and variability.

could prepare DFBA emulsion with an average droplet size of 134.5±2.5 nm, and a zeta potential of -7±1.5 mV (F1). Size and zeta potential of F2 was 219±4.3 nm and -6.4±1.9 mV, respectively. Nature of the dialysis membrane and the molecular weight cut off of dialysis bag have a significant effect on the release profile of the different difluprednate emulsions. DFBA released fast with the increase in molecular weight cut off of dialysis bag and highest drug release was noted with 50 kD RC as compared to the other membranes. Whilst the drug release profiles of F1 and F2 were overlapping, drug release from F1 and F2 was slower with 20 kD CE membrane.”

\(^{11}\) 2016 FDA Resp. at 31.

\(^{12}\) 21 C.F.R. §§ 314.94(a)(7), 320.1(g).
Replicates from each lot analyzed should also be submitted to provide a picture of variability.\textsuperscript{13}

3. **Conclusion**

RESTASIS is a complex, heterogeneous, multi-phase dosage form (containing an oil phase, an aqueous phase, an interface consisting of surfactants and other stabilizing polymers, and micellar structures). Drug is distributed in each of these phases; the amount of drug in each phase can shift based on external environment (both related to manufacturing and to post-administration biological interactions\textsuperscript{14}); and the amount of drug in each phase may influence product bioavailability, safety, and effectiveness. Allergan has submitted data to FDA demonstrating the in vivo relevance of distribution patterns, and potential risks that may accompany drug variations compared to RESTASIS. For these reasons alone, any proposed generic comparison to RESTASIS cannot be lightly undertaken.

Allergan requests that FDA address each of the comments submitted in this document. We believe that further revisions to the October 2016 Draft Guidance are necessary, and that further public elucidation of the standards FDA intends to apply is appropriate, from both scientific and regulatory perspectives.

Sincerely,

\[\text{Signature}\]

Dwight O. Moxie
Vice President,
Assistant General Counsel

Attachments

\[\text{Notes:}\]
\textsuperscript{13} A distinct draft guidance related to difluprednate ophthalmic emulsion states, for example: “[ANDA] applicants should provide no less than 10 datasets from 3 batches each of the Test and Reference products to be used in the PBE analysis.” An ANDA applicant for cyclosporine ophthalmic emulsion will have to determine and validate the appropriate number of replicate analyses.

\textsuperscript{14} 2014 Petition at 17.
Alternative Approaches to Demonstrate Bioequivalence of Ophthalmic Products and the Role of Regulatory Science

Stephanie H. Choi, Ph.D.
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

- 48 products (58%)
- 35 products (42%)
- 11 products (21%)

41 products have generics approved under ANDA (505(j))
3 products have TEs approved under NDA (505(b)(2))
8 products do not have any multisource products

Total non-solutions: 52 products
Total solutions: 83 products
# Approved Ophthalmic Therapeutic Equivalents: Non-Solutions

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## Approved Ophthalmic Therapeutic Equivalents: Non-Solutions

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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

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• 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
    - 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

A

B

C

D

\[ \text{Onset: } 15.91 \text{ Pa} \]

\[ \text{Onset: } 7.013 \text{ Pa} \]

\[ \text{Onset: } 3.755 \text{ Pa} \]
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
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

<table>
<thead>
<tr>
<th>Dilution Factor</th>
<th>Histogram (Intensity, % vs. Size, nm)</th>
<th>Z-Average (d. nm) 0.89 cP viscosity</th>
<th>PdI</th>
<th>Intensity Peaks (d. nm, % Intensity)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1X</strong></td>
<td><img src="image" alt="Histogram" /></td>
<td>301.2 ± 11.4</td>
<td>0.56 ± 0.03</td>
<td>877.6 (52%) 260.5 (39%) 67.1 (9%)</td>
</tr>
<tr>
<td><strong>10X</strong></td>
<td><img src="image" alt="Histogram" /></td>
<td>103.7 ± 0.9</td>
<td>0.28 ± 0.01</td>
<td>180.0 (67%) 53.6 (33%)</td>
</tr>
<tr>
<td><strong>100X</strong></td>
<td><img src="image" alt="Histogram" /></td>
<td>101.2 ± 1.3</td>
<td>0.27 ± 0.01</td>
<td>149.7 (78%) 46.3 (22%)</td>
</tr>
</tbody>
</table>
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


• Product-Specific Recommendations for Generic Drug Development
Preparation and Evaluation of Difluprednate Topical Ocular Emulsions
S. Palakurthi 1, D. Cai 1, J. Qiu 1, M. Absar 2, S. Choi 2
1 Texas A and M College of Pharmacy, 2 U.S. Food and Drug Administration

Purpose
Currently there is no specific compendial assay for dissolution for topical ophthalmic emulsion formulations. Durezol®, a topical emulsion of difluprednate, is used for the treatment of postoperative inflammation and pain. Difluprednate (DFBA) is insoluble in water and its systemic absorption was shown to be very limited. This study sought to develop in vitro testing methods to be used in comparison for different formulations of DFBA, and the in vitro tests should be able to discriminate the drug products and be able to predict the clinical efficacy of the product. Aim of the present study was to develop formulations similar to Durezol®; (with the same quality and quantity of ingredients), and develop an appropriate dissolution method that can discriminate the product and formulation variables of difluprednate topical ocular emulsion and also predict the bioequivalence of the generic products.

Methods
The difluprednate emulsion was prepared in two steps. As the first step, the difluprednate coarse-emulsion containing 0.05% difluprednate, caster oil as an oil phase and polysorbate 80 as an emulsifying agent was produced with PolyTron mixture system at 70 °C and 12000 rpm for 1 h. Then the coarse-emulsion was subjected to a high-pressure emulsification (Microfluidizer M-110P) at 10,000 and 30,000 psi pressure for 10 volume cycles. Two emulsion formulations (F1, 134.5±2.5 nm; F2, 219±4.3 nm) were prepared. The particle size and zeta-potential of the emulsion were characterized through dynamic light scattering analysis using a Brookhaven ZetaPALS zeta potential analyzer at 25 °C. In vitro release behaviors of Durezol and prepared difluprednate emulsions (F1 and F2) were investigated by dialysis method using dialysis membranes of different nature (CE, Cellulose Ester; and RC, Regenerated Cellulose) and molecular weight cut off (10, 25 and 50 KD) with 0.05% SLS as the dissolution medium. A 1 mL of emulsions was accurately placed into dialysis bag and the bag was suspended in 75 mL of 0.5% sodium lauryl sulphate (SLS) in phosphate buffered saline (PBS) as the dissolution medium. A 1 mL of dissolution medium was withdrawn at predetermined time intervals up to 96 h and the same volume of fresh release medium was added to maintain a constant volume. The concentrations of difluprednate in the samples was determined by a HPLC method. The statistical analysis was performed with Student’s t test. P<0.05 was considered statistically significant.

Results
Mean droplet size of Durezol®; was found to be 137.8±2.8 nm. We could prepare DFBA emulsion with an average droplet size of 134.5±2.5 nm, and a zeta potential of -6.7±1.5 mV (F1). Size and zeta potential of F2 was 219±4.3 nm and -6.4±1.9 mV, respectively. Nature of the dialysis membrane and the molecular weight cut off of dialysis bag have a significant effect on the release profile of the different difluprednate emulsions. DFBA released fast with the increase in molecular weight cut off of dialysis bag and highest drug release was noted with 50 kD RC as compared to the other membranes. Whilst the drug release profiles of F1 and F2 were overlapping, drug release from F1 and F2 was slower with 20 kD CE membrane.

Conclusion
DFBA ophthalmic emulsion formulations with different droplet size were prepared and their stability was characterized. A dialysis method was developed to differentiate drug release from F1 and F2 formulations. Studies are in progress to further differentiate the release profiles form F1 and F2 formulations using a variety of other methods.

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