August 17, 2013

*Via Hand and Electronic Delivery*

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

Cyclosporine Ophthalmic Emulsion, 0.05%

Dear Sir or Madam:

Allergan, Inc. respectfully requests that the Food and Drug Administration (“FDA”) revise and replace the above-referenced draft guidance published on June 20, 2013 (the “Draft Guidance”). The Draft Guidance recommends that in vitro analyses alone be submitted to establish that a proposed generic drug product is bioequivalent to Allergan’s RESTASIS® (cyclosporine) ophthalmic emulsion, 0.05% w/v (“RESTASIS”). For reasons explained below, that proposal is unsound both scientifically and legally. Allergan therefore requests that FDA replace the Draft Guidance with a revised guidance document that explains in vivo comparative clinical studies are required to demonstrate that a proposed generic product is bioequivalent to RESTASIS. That position must be applied in the agency’s decisionmaking and practice.

---

1 See 78 Fed. Reg. 37,230 (June 20, 2013).
For convenience of review, the contents of this comment are identified here:

I. Summary of Objections ........................................................................................................................................ 4

II. Background .......................................................................................................................................................... 9

   A. Dry Eye Disease (Keratoconjunctivitis Sicca) Is a Serious Condition that Requires Safe and Effective Treatment ................................................................................................................. 9

   B. RESTASIS Is a Complex Product That Was Developed to Address an Extremely Challenging Medical Need .................................................................................................................................. 10

       1. The Achievement of RESTASIS ................................................................................................................ 10

       2. The Public Health Importance of Product Reliability .................................................................................. 12

       3. RESTASIS Was Formulated Specifically to Function in the Unique and Challenging Ocular Environment .................................................................................................................. 13

       4. The RESTASIS Formulation is A Complex Emulsion That Attains Safe and Effective Deposition of Cyclosporine in the Eye ........................................................................ 14

       5. Changes in Physicochemical Parameters of Emulsion in Presence of Tears (in vitro assessment) ................ 17

III. FDA Has Recognized It Lacks Scientific Evidence to Support the Draft Guidance ........................................... 17

   A. FDA Has Long Recommended In Vivo Testing For Topical Emulsions Based On the Available Science ........................................................................................................................................ 17

   B. FDA Has Failed to Establish A Scientific Basis for In Vitro Methods to Establish Bioequivalence of Topical Emulsions .................................................................................................. 20

IV. Scientific Evidence Demonstrates FDA’s Draft Guidance Would Permit Non-Bioequivalent Products To Be Deemed Bioequivalent ......................................................................................... 23

   A. Under the In Vitro Option, Drugs Differing In Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy Would Be Considered Bioequivalent .................................................................................. 23

   B. The In Vitro Approach Cannot Reliably Measure Drug Distribution Throughout the Emulsion—Which Is Essential for Bioequivalence ........................................................................... 24

2. Additional Limitations of Globule Size Distribution and Viscosity Measurements May Cause Dissimilar Products to Appear the Same. ............................................................................................................. 27

3. Additional Testing, Including In Vivo Testing, is Needed to Address the Shortcomings of the Draft Guidance’s In Vitro Option............................ 28

C. There Is No In Vitro Drug Release Methodology Established for RESTASIS or to Characterize Ophthlamic Emulsions......................................................... 29

D. Current Drug Release Methods for Disperse Systems Are Not Designed To Capture Key Characteristics of RESTASIS................................................................. 30

E. In Vitro Drug Release Testing Cannot Simulate the Complex Drug Release and Delivery to Receiving Compartments (Ocular Tissues). ........................................... 31

V. A Clinical Endpoint Study Is Required Because Product-Specific Factors and the Precise Mechanism of Action of RESTASIS are Unknown to the Scientific Community .................................................................................................................................. 32

VI. An In Vivo Approach to Bioequivalence is Required as a Matter of Public Health......... 34

VII. The Draft Guidance Is Inconsistent With The FDCA And FDA Regulations and Contrary to the APA Requirement of Reasoned Decisionmaking................................. 36

A. The In Vitro Approach Proposed in the Draft Guidance Violates the FDCA. ........ 36

B. FDA Is Bound By Its Own Regulations to Require In Vivo Testing Here................. 39

C. FDA Has Long Required In Vivo Testing For Topical Emulsions and It Cannot Change Its Position Without a Reasoned Explanation. .......................................... 41

D. Any Approval Made In Accordance With the Draft Guidance Would Be Arbitrary and Capricious.......................................................................................... 41

VIII. Conclusion ......................................................................................................................... 43
I. Summary of Objections

The Draft Guidance is a sharp and unjustified break from FDA’s consistent past practice. Until now, FDA has recognized that the only scientifically valid way to demonstrate that a proposed generic drug is bioequivalent to an ophthalmic emulsion such as RESTASIS is to conduct comparative clinical trials to demonstrate equivalent safety and effectiveness based on clinical endpoints. FDA’s longstanding position was—and is—necessitated by basic scientific principles; the new position reflected in the Draft Guidance, however, is contrary to current science as well as applicable law.

The law requires any applicant to submit evidence that its proposed generic product is “bioequivalent” to RESTASIS. This bioequivalence requirement is the statutory cornerstone of the abbreviated new drug application (“ANDA”) review process: it provides the fundamental guarantee that a generic drug (which is not otherwise evaluated in clinical trials to demonstrate safety and effectiveness for an intended use) will be safe and effective for use by patients and may be appropriately interchanged with the innovator drug.

If a drug acts through absorption into the bloodstream, bioequivalent drug products are those that show no significant difference in the rate and extent of absorption of the therapeutic ingredient.\(^2\) For a drug like RESTASIS that is not intended to be absorbed into the bloodstream:

- “[T]he 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”\(^3\); or
- “[T]he Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.”\(^4\)

There is, however, no currently available scientifically valid method for measuring bioavailability in vivo for a drug like RESTASIS that is applied topically to, and acts locally in, the eye. (In other words, the first option above is not satisfied.) Furthermore, there is no currently available scientifically valid in vitro method (as proposed in the Draft Guidance) that can be used as a surrogate to detect any significant differences in safety or therapeutic effect. (In other words, the second option is also not satisfied.)

To the contrary, Allergan has manufactured and tested several experimental products that are close variations of RESTASIS and conform to the Q1/Q2 and physicochemical criteria set forth in

the Draft Guidance but that are *not* bioequivalent to RESTASIS. As discussed below, deeper laboratory, human corneal epithelial cell, and animal pharmacokinetic and tolerability studies show that the Draft Guidance is inadequate to ensure bioequivalence in human patients. Perhaps one day science will advance to a point where an in vitro method will be validated as a way to ensure in vivo bioequivalence for an opthalmic emulsion like RESTASIS. But at present no such method exists. No shortcut is possible, and the only way to demonstrate that a proposed generic is bioequivalent to RESTASIS is to conduct a comparative human clinical trial that demonstrates appropriate safety and therapeutic effect.

**The Proposed In Vitro Measurements Are Inadequate to Show Bioequivalence From Both Scientific and Legal Standpoints**

The bioequivalence requirement is the statutory cornerstone of the ANDA approval process for good reason. Taking scientifically unjustified shortcuts around this critical requirement shortchanges patients and physicians who depend on RESTASIS’s proven safety and effectiveness, and it risks undermining public confidence in generic drugs more broadly.

The Draft Guidance outlines a handful of physicochemical drug characteristics and suggests that, where these characteristics are present in vitro (i.e., laboratory testing alone), FDA may infer that a proposed generic drug is bioequivalent to RESTASIS without ever analyzing the product in patients. That position is demonstrably incorrect. The eye is an especially complex organ; the site of action is poorly understood for dry eye therapeutics with an anti-inflammatory mechanism of action (for example, how multiple tissues interact with drug differentially); and emulsions are an especially complex dosage form. The physicochemical parameters proposed in the Draft Guidance have not been established as a valid scientific measure of the rate and extent of absorption of cyclosporine in relevant ocular tissues. Nor have they been established as valid methods to detect a significant difference between a generic drug and RESTASIS in terms of safety or therapeutic effect. Because of RESTASIS’s complex nature, requiring that the proposed generic have the same active ingredient and the same inactive ingredients is inadequate to ensure that the generic will actually perform the same way in patients. Selecting certain physicochemical parameters to assess in vitro simply does not compensate for that inadequacy.

The fundamental challenge is that emulsions—and especially emulsions operating in the complex environment of the eye—are too complex and too poorly understood to know at this point which parameters to assess, or how to assess them, to ensure in vivo bioequivalence. As a result, FDA lacks a scientific basis to devise in vitro methods that are adequate and valid to assess the totality of factors relevant to bioavailability and bioequivalence of RESTASIS. Using incomplete parameters with presently *untested and unproven* relationships to bioavailability as surrogates to infer bioequivalence is unsound.

---

5 Allergan did not perform in vitro release tests on these experimental formulations. As discussed in Section IV.C below, no in vitro release test exists for RESTASIS, and none has been established or validated for an opthalmic emulsion.
FDA’s proposed approach lacks sufficient scientific guideposts and lacks in vitro/in vivo correlation (“IVIVC”) of its selected (but incomplete) parameters.\(^6\) On its face, the Draft Guidance fails to adequately consider the complexity of topical ophthalmic emulsions composed of multiple phases with varied components, including free drug, diverse drug-containing globules and micelles, and other structures of many varying sizes and types (collectively described in this document as “globules”) that are stabilized by various, dynamic molecular interactions. The Draft Guidance fails to require an accurate profile with respect to key characteristics that impact the dynamic equilibrium within the emulsion (e.g., there is no requirement to develop a rheology profile that takes into account the effect of shear forces on polymer components). It also fails to account for the complex and largely unknown manner in which RESTASIS interacts with the ocular tear fluid, the physical barriers, multiple tissues, and the dynamic environment of the human eye. Where any of these product characteristics, interactions, and known or unknown factors influencing those interactions differ, there is no reasonable basis to assume that bioavailability will not also differ.

In addition, the Draft Guidance’s heavy reliance on the measurement of globule size is misplaced. Common methods for measuring globule size cannot be relied upon to detect submicron-size structures that contain a substantial portion of the drug in RESTASIS. Globule size also is an unreliable surrogate for bioequivalence because measurement is highly technique-dependent (i.e., results can be directly impacted by the manner in which the test is performed), and the parameters for the proposed analyses can be selected or so as to show similarity of emulsions that are actually dissimilar.

**Allergan Has Demonstrated Significant Differences Among Formulations That Conform to the Draft Guidance**

The burden rests on an ANDA applicant to affirmatively demonstrate bioequivalence of its proposed product to RESTASIS—and on the agency to justify a change in its position and to show that its new position satisfies applicable legal standards. It does not fall on Allergan to affirmatively prove that drug formulations that conform to the Draft Guidance are not in fact bioequivalent to RESTASIS.

But if empirical confirmation is needed that the Draft Guidance is inappropriate, Allergan can provide it: Allergan manufactured and tested multiple experimental emulsion formulations that conform to the Draft Guidance criteria. These research data—which Allergan has summarized in Sections IV.A through IV.C below, and is submitting to FDA for review in full\(^7\)—show that

---

\(^6\) IVIVC means the ability to predict, accurately and precisely, expected bioavailability characteristics from specified in vitro characteristics. Allergan acknowledges that certain in vitro analyses are performed in its approved manufacturing process for RESTASIS. However, the Allergan specifications are quality control measurements used to ensure that the clinically-proven, validated manufacturing process continues to yield consistent results. This is a very different use than the proposal to use physicochemical characteristics as an indicator of bioequivalence.

\(^7\) The full data are being submitted today in a separate correspondence to the RESTASIS NDA 50-790. That separate correspondence is confidential, due to the trade secret and confidential commercial information revealed therein.
seemingly comparable emulsions satisfying the Draft Guidance’s criteria nevertheless demonstrate such variability that bioequivalence to RESTASIS in humans is highly unlikely.

- Certain experimental emulsions that conformed to the Draft Guidance in vitro criteria nonetheless exhibited measurable differences from RESTASIS with respect to drug distribution inside the emulsion.\(^8\)

- Pharmacokinetic studies in rabbits and dogs demonstrated that drug exposure from some test emulsions was nine times higher, and delivered at different time rates, as compared to RESTASIS. Different drug concentrations also were measured in tears, suggesting different availability and uptake by relevant ocular tissues.\(^9\)

- Increased severity of ocular discomfort and conjunctival hyperemia was observed in rabbits receiving certain test formulations as compared to RESTASIS. This suggests a different tolerability profile compared to RESTASIS.\(^10\)

Rather than simply assuming (contrary to the evidence) that such differences would not have clinical importance in long-term use in patients, FDA must instead require up-front, in vivo testing in humans to demonstrate appropriate clinical safety and effectiveness equivalent to the proven reference listed drug RESTASIS.

Nor is there any pressing need to relax the bioequivalence requirement to accelerate the availability of generic alternatives to RESTASIS. RESTASIS is widely available (including through a patient assistance program for patients who need financial assistance), and it has been demonstrated to be safe and effective for its intended use. RESTASIS is distributed worldwide, and millions of people have used it over the last ten years to slow or halt dry eye disease.

Dry eye is a serious, progressive disease, and failure to treat it, or treatment with ineffective medication (for example, a formulation that inadequately delivers drug to the pertinent ocular tissues), could lead to increased inflammation, significant damage to the eye, and complications including vision loss. A generic version that mimics certain in vitro properties of RESTASIS without actually being bioequivalent to RESTASIS represents a clear potential threat to patient safety.

Accordingly, while Allergan fully appreciates the need to balance encouraging innovation in drug development with making generic drugs readily available to the public when scientific and legal standards for ANDA approval are satisfied, the Draft Guidance’s proposal to rely solely on in

\(^8\) See Section IV.B below.

\(^9\) See Section IV.A below.

\(^10\) See Section IV.A below.
vitro testing for proposed generic equivalents to RESTASIS is unnecessary, unjustified, and potentially unsafe. In addition, against a backdrop of already-existing concerns regarding the equivalence of ophthalmic generic drugs to reference listed drugs more generally, FDA’s proposal carries a high potential to erode patients’, physicians’, and the public’s confidence in generic formulations and the adequacy of FDA’s generic drug approval system.

**Clinical Studies Of Safety and Effectiveness Are Required**

Without any scientific basis to correlate in vitro measurements—the ones specified in the Draft Guidance or any others—with actual impact on bioavailability, the only scientifically valid method to ensure bioequivalence is in vivo testing, i.e., through clinical studies. Merely altering or augmenting the in vitro testing parameters laid out in the Draft Guidance will not solve the fundamental problem of relying solely on in vitro testing.

FDA itself has acknowledged that the current state of understanding of ophthalmic emulsions is insufficient to justify the in vitro approach proposed by the Draft Guidance, as a matter of scientific principle. FDA acknowledged just last year that the scientific foundation for relying on in vitro testing to assess bioequivalence of ophthalmic emulsions is “lacking,” and FDA thus requested new research on that subject. As this Comment explains (see Section III.B, below), the still incomplete study that FDA commissioned to fill that void has yielded more questions than answers, and more research will be required to achieve the kind of understanding of ophthalmic emulsions that would be needed to justify a change in policy.

**FDA Must Revise the Draft Guidance to Protect Patients and to Comply with the Law**

Ultimately, FDA’s Draft Guidance lacks scientific justification, creates risk that patients will be exposed to products of unknown safety or effectiveness, and is inconsistent with the applicable legal standards. If FDA were to find that a generic drug is bioequivalent to RESTASIS without requiring in vivo testing, FDA’s action would violate the Federal Food, Drug, and Cosmetic Act (“FDCA”), its implementing regulations, and basic principles of administrative law requiring reasoned decisionmaking. For a locally acting ophthalmic emulsion, there are no scientifically valid in vitro methods to show bioequivalence that can reasonably be expected to detect significant differences in safety and therapeutic effects between a proposed generic drug and RESTASIS. The Draft Guidance thus violates 21 U.S.C. § 355(j)(8)(A)(ii). Moreover, to establish such a method under that statutory authority, FDA would have to proceed by notice-and-comment rulemaking and other transparent, rigorous processes (e.g., generation and publication of the alleged scientific basis for the proposed method so it can be assessed by knowledgeable stakeholders; advisory committee consultation)—not, as here, on the basis of an informal, nonbinding guidance document, breaking with past practice without justification.

For all these reasons, the Draft Guidance is fundamentally defective as a matter of both science and law, and FDA should replace it with a revised guidance that explains that comparative clinical trials are required to demonstrate equivalent safety and effectiveness for a proposed generic referring to RESTASIS.
II. Background

A. Dry Eye Disease (Keratoconjunctivitis Sicca) Is a Serious Condition that Requires Safe and Effective Treatment

Dry eye disease, also named keratoconjunctivitis sicca, is among the leading causes of patient visits to ophthalmologists in the United States.\(^\text{11}\) Twenty-three million Americans suffer from dry eye disease, which has two main causes: decreased secretion of tears by the lacrimal (tear-producing) glands, and loss of tears due to excess evaporation.\(^\text{12}\) Both causes lead to ocular discomfort, often described as a feeling of dryness, burning, a sandy/gritty sensation, or itchiness. Visual fatigue, sensitivity to light, and blurred vision are also characteristic of the disease. This is a serious disorder that, if left untreated or undertreated, progressively damages the ocular surface and may lead to vision loss.\(^\text{13}\)

Dry eye disease is a disorder of the “tear film,”\(^\text{14}\) and ocular inflammation is known to play a major role in the symptoms and progression of the disease. Dry eye disease patients can suffer mild irritation (Level 1 severity). In patients with Level 2 to Level 4 severity scores, the symptoms are quite debilitating.\(^\text{15}\) If the condition in these cases is untreated or treated inadequately (e.g., only with an agent such as artificial tears), the disease will continue to progress, and may lead to severe eye damage and vision loss.\(^\text{16}\) Severe problems with

---


\(^{12}\) Aging is one of the most common causes of dry eye, because tear production often decreases as one ages. Dry eye affects more women than men because hormonal changes, such as those that occur in pregnancy, menstruation, and menopause, can decrease tear production. (Meadows M. Dealing with Dry Eye. FDA Consumer Magazine. U.S. Food and Drug Administration. (May–June 2005) [archived from the original on February 23, 2008].) Significant risk factors for dry eye disease also include autoimmune diseases such as arthritis, lupus, and Sjögren’s syndrome (a more severe and chronic form of dry eye disease), and medical conditions such as diabetes.


\(^{14}\) The eye surface is supported and maintained by the tear film, which is composed of three components (lipid, aqueous, and mucin) that make up two fluid layers. Holly F.J. Dry eye and the Sjögren’s syndrome. Scand J Rheumatol Suppl. 1986;61:201-205. Normal healthy tears contain a complex mixture of proteins and other components that are essential for ocular health and comfort. Tears provide nutrients and support the health of cells in the cornea, lubricate the ocular surface, and protect the exposed surface of the eye from infections. Clear vision depends on an even distribution of tears over the ocular surface. Dry eye disease affects the eye surface and changes the tear film composition dramatically. Typical changes include an elevated tear osmolarity, aqueous deficiency, altered mucins and lipid layer, and an altered proteomic profile.

Individuals of all ages who present with symptoms and signs suggestive of dry eye – such as irritation, redness, fluctuating vision, and decreased tear meniscus – should be evaluated to identify the causes of dry eye; establish an appropriate diagnosis; determine appropriate therapy; relieve discomfort; and prevent complications, such as loss of visual function, infection, and structural damage. (American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Patterns Committee. Dry Eye Syndrome. Limited Revision. San Francisco (CA): American Academy of Ophthalmology; 2011.) The treatment of dry eye may include education and environmental modifications; elimination of offending topical or systemic medications (where feasible); topical medication; systemic medication; surgery; and other treatment.


untreated dry eye can also lead to corneal infection and scarring.\textsuperscript{17} Compared across different diseases, dry eye was found to cause degradation in quality of life that is on par with other severe disorders, such as class III/IV Angina.\textsuperscript{18}

B. RESTASIS Is a Complex Product That Was Developed to Address an Extremely Challenging Medical Need

1. The Achievement of RESTASIS

At the time Allergan initiated the RESTASIS development program in 1992, dry eye was a largely unmet medical need, predominantly affecting women. No therapeutic treatments were available, apart from the use of artificial tears and, for the most severe cases, blockage of the lacrimal drainage system with punctal plugs or cauterization.

Allergan’s investigators completed seminal work in the dry eye disease area, identifying the role of the T-cell and chronic inflammation in the pathogenesis of dry eye disease,\textsuperscript{19} followed by application of cyclosporine (a drug previously used systemically to prevent transplant rejection) to target the disease locally. The lipophilic nature of cyclosporine, however, made it extremely difficult to formulate an ocular-friendly preparation with appropriate bioavailability. The multiple target tissues of the ocular surface (cornea, conjunctiva, lacrimal glands, etc.), the composition of the tear film (not a simple salt solution), and the short retention time on the eye contributed many complex issues in creating an efficacious formulation. Various formulations were attempted with concentrations up to 2% cyclosporine and were poorly tolerated and absorbed. Ultimately, Allergan successfully formulated RESTASIS in its current form. The clinical development program then followed.

The approved RESTASIS indication was based on statistically significant benefits in each of two pivotal clinical studies in which efficacy was defined as an improvement in the amount of tears produced (measured with a Schirmer score with anesthesia of > 10 mm / 5 min, from a baseline of 0-5 mm). As a normal value for Schirmer’s wetting is 10 mm / 5 min, an improvement of > 10 mm / 5 min assured that responders achieved a total reversal of this measure of disease (i.e., a complete response) regardless of their baseline measurements. It should be noted that an established severity scheme was not available at the time the trials were begun. Using a more recently established grading scheme,\textsuperscript{20} Allergan determined that as many as 60% of the enrolled

\textsuperscript{17} Meadows, supra note 12.


patients in its pivotal trials were in the most severe, Level 4 severity category, and many of those patients may have been refractory to a single intervention or required longer dosing to achieve benefit.\textsuperscript{21} Despite the severity of disease at baseline, and the very high hurdle for success, the proportion of patients experiencing a complete response was three-fold higher among subjects taking RESTASIS compared with those taking vehicle (15\% versus 5\%) after 6 months of treatment. This was a highly significant result (p<.007).

An additional responder analysis based on a composite score that included the key endpoints in dry eye (corneal staining, Schirmer with anesthesia, blurred vision, and REFRESH\textsuperscript{®}(artificial tear) use) showed that the response rate to RESTASIS in these rather severe patients was quite robust. In each study, 43 to 50\% of patients taking RESTASIS were classified as responders, compared to only 30\% of patients taking vehicle, and these results were statistically significant in both studies (see Table 1, reproduced from RESTASIS NDA 21-023). Further evidence of a direct therapeutic response that was related to the mechanism of action of RESTASIS was found on the expression of the inflammatory marker HLA DR\textsuperscript{22}, which is expressed in a greater amount on conjunctival epithelial cells in the presence of inflammation. In a sub-study within the pivotal trials, expression of HLA-DR was highly significantly reduced after RESTASIS treatment at months 3, 6, and 12 compared with baseline values, both in the percentage of positive cells and in the level of protein expression, whereas vehicle did not induce any change in HLA DR expression over time (NDA). Further evidence of RESTASIS’s benefit on the ocular surface was also seen in the number of goblet cells in the conjunctiva. The goblet cells are the major producer of the mucin layer of the tear film and are critical for maintaining tear film stability. In severe dry eye, the conjunctival epithelium shows a reduction in goblet cell numbers due to the presence of inflammation.\textsuperscript{23} In the same sub-study, there was a 191\% increase (P = 0.014) in goblet cell number with RESTASIS, compared to a 13\% increase with vehicle, at month 6. These results further support the significant reduction of conjunctival inflammation by RESTASIS in moderate to severe dry eye disease and that clinical meaningful benefits are experienced by a substantial proportion of treated patients.

\textsuperscript{21} DEWS, supra note 15


Table 1: Number and Percent of Responders in Phase 3 Studies (Intent-to-Treat Population)  
(Abstracted from RESTASIS NDA 21-023)

<table>
<thead>
<tr>
<th>Study 192371-002</th>
<th>Study 192371-003</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CsA 0.05%</strong></td>
<td><strong>Vehicle</strong></td>
</tr>
<tr>
<td><strong>CsA 0.05%</strong></td>
<td><strong>Vehicle</strong></td>
</tr>
<tr>
<td><strong>Month 6</strong></td>
<td><strong>Month 6</strong></td>
</tr>
<tr>
<td>50% (58/116)</td>
<td>31% (34/109)</td>
</tr>
<tr>
<td>43% (58/136)</td>
<td>29% (38/130)</td>
</tr>
</tbody>
</table>

CsA = cyclosporine ophthalmic emulsion. The numerator is the number of responders and the denominator is  
the number of patients,

a Among-group P values from Fisher’s exact test.

b Pairwise comparisons (from Fisher’s exact test) favored 0.05% vs vehicle.

c Pairwise comparisons (from Fisher’s exact test) favored 0.05% vs vehicle.

2. The Public Health Importance of Product Reliability

FDA’s application of the approval standards for RESTASIS generics is a matter to be carefully  
addressed. Thanks to extensive research and development plus clinical studies, FDA and  
patients can expect that RESTASIS will increase tear production in patients whose tear  
production is presumed to be suppressed due to ocular inflammation associated with dry eye  
disease. This confidence is imperative for generic products as well.

Dry eye is a progressive disease. The utility of RESTASIS in preventing progression of dry eye to  
a worse severity category was demonstrated in a recent independent clinical study of 58  
patients with level 2/3 severity disease, similar to the reanalysis population described above.24  
Treatment of symptoms alone with REFRESH® artificial tears, or replacement of cyclosporine  
0.05% therapy with REFRESH® artificial tears, allowed continued progression of the disease and  
an increase in disease severity.25 Although milder forms of dry eye disease may respond to  
treatments like artificial tears that alleviate symptoms without modifying the disease process,  
RESTASIS is directed towards treating the underlying disease process in moderate to severe  
patients.26

It is also significant that there is an appreciable response lag time associated with the initiation  
of RESTASIS treatment (3-6 months post-initiation). This presents yet another reason why FDA  
must apply valid science in ensuring the bioequivalence of proposed generic products. An  
ineffective product may mean that treatment is delayed or denied. As discussed above, the  
progressive nature of dry eye disease cautions in favor of conservatism, even where the facts  
(unlike here) might arguably support a novel analytical approach.

24 Rao, supra note 16.

Pharmacokinet. 2005;44:247-261; Rao, supra note 16; Rao S. Reversibility of dry eye deceleration after topical cyclosporine 0.05%  

26 DEWS, supra note 15.
3. **RESTASIS Was Formulated Specifically to Function in the Unique and Challenging Ocular Environment**

The specific target organs of RESTASIS are understood to be the external tissues of the eye. But the required amount of drug in individual eye tissues (e.g., the lacrimal gland, conjunctiva, or epithelial layers of the cornea) to obtain relief of symptoms is not known. Nonetheless, the RESTASIS emulsion has been shown through clinical studies to achieve the requisite tissue concentrations and time course for safety and effectiveness.

Delivery to the relevant ocular tissues was one of RESTASIS’s core innovations. A complex emulsion was required to deliver the drug appropriately to the tissues. Unlike other drug delivery routes, a topical ophthalmic formulation usually delivers drug to the ocular tissues in a relatively short timeframe of a few minutes. An eye-drop, irrespective of the instilled volume, often eliminates rapidly within five minutes after administration, and only a small fraction (<3%) of the drug substance is delivered to the tear film and/or is absorbed and becomes bioavailable in ocular tissues. More than 75% of an applied topical ophthalmic formulation is lost via nasolacrimal drainage, and hence ocular drug availability is very low.

Normal human tear turnover is approximately 16% per minute, and this turnover acts to remove drug solution from the conjunctival cul-de-sac. Turnover may also be stimulated by many other factors including ocular irritation, which renders topical application of ophthalmic solutions to the cul-de-sac imprecise and extremely inefficient.

Formulation excipients and excipient quality can stimulate tear production and dilution, which may further enhance drug elimination. Simple dilution of instilled drug in the tears acts to reduce the transcellular availability and flux of drug that remains in the conjunctival cul-de-sac.

Bioavailability of topically applied cyclosporine is a result of complex differential rate processes and precorneal film dynamics that adjust continually toward equilibrium:

1. Precorneal clearance of the applied dose (e.g., due to blinking and lacrimation)
2. Tear film drug concentration time curve (i.e., amount of cyclosporine in the tears)
3. Tissue permeability
4. Post tissue clearance

---

27 This is unlike the area of dermatology, where a single tissue is the target for drug delivery.
The precorneal and corneal factors that affect ocular bioavailability and systemic absorption significantly impact the bioavailability of complex topical dosage forms such as an emulsion. No release method exists today that can differentiate performance in the rapid time scales required. The precorneal half-life is on the order of minutes. Given analytical variability in an in vitro release study that simulates this short timeframe, differentiation of a good formulation and a poor formulation is unlikely. Furthermore, science has not yet progressed enough to enable anyone to create an in vitro process that accurately mimics emulsion globule coalescence and break-up in the tear film.

4. The RESTASIS Formulation is A Complex Emulsion That Attains Safe and Effective Deposition of Cyclosporine in the Eye

RESTASIS is a complex, oil-in-water, ophthalmic emulsion that delivers the topical immunomodulator, cyclosporine, to the surface of the eye for low concentration absorption and therapeutic effect.31 The emulsion allows cyclosporine concentrations to penetrate directly into the ocular tissues in therapeutic amounts, with no detectable systemic absorption in the blood that could pose a safety concern.

Certain challenges of drug delivery to external tissues of the eye were described above.32 To achieve an effective and safe rate and extent of absorption, the drug product must accurately and differentially interact with each relevant tissue and the tear composition of a diseased eye that may change over the timecourse of the disease. In addition, the topical ophthalmic formulation must deliver and release its active ingredient to relevant ocular tissues in a timeframe of mere minutes (a product engineering challenge).33 Because ocular drug availability is extremely low,34 there is little or no margin for error.

That RESTASIS is an emulsion is a critical fact to the present analysis. An emulsion is a dispersion of two or more immiscible liquids, stabilized by a surfactant or emulsifier coating droplets and preventing coalescence by reducing interfacial tension or creating a physical repulsion between the droplets.35 Although emulsions are often depicted schematically as drug containing oil droplets coated with a surfactant/emulsifier and dispersed in an aqueous phase, they are fundamentally complex dosage forms. The emulsion components can distribute themselves in various phases depending on their physicochemical properties as well as the process of manufacture of the emulsion. For example, the surfactant can partition into the

31 The cyclosporine in RESTASIS acts by inhibiting T cell activation and inhibiting pro-inflammatory cytokine secretion within the tissues of the ocular surface, including the cornea, conjunctiva, eyelid/meibomian glands, accessory lacrimal glands, and the regional draining lymph nodes. (Product Monograph for RESTASIS, 2010).


33 Maurice and Mishima, supra note 28.

34 Schoenwald, supra note 30.

water phase to form micelles in addition to acting as an emulsifier to stabilize oil droplets. The oil droplets may form globules with a range of sizes.

The drug dissolved in the oil can partition into the other phases, such as the water phase, micellar phase, microemulsion phase, or at the oil/water interface. The drug is thus expected to be present in the product in several locations including:

- in true solution in water
- in micellar equilibrium in the aqueous phase (in both the micellar core and in the surfactant palisade layers)
- in the oil droplets
- in the surfactant monolayer of the oil/water interface
- associated with viscosity agents

The portion of the drug in each of these phases depends on physicochemical properties of the drug, the emulsion composition, and importantly the manufacturing process. This has been demonstrated for phospholipid containing emulsions, and it has been shown that process changes impact the distribution of drugs in these phases.

The following schematic depicts the complexity of RESTASIS emulsion.

---


In RESTASIS emulsion, castor oil (oil phase) is dispersed in the water phase using polysorbate 80 as the surface active agent. In addition, the water phase contains a secondary emulsifier and viscosity agent (carbomer polymer), which provides further stability to the emulsion droplets over the product shelf life.

Polysorbate 80 is a strong surfactant with a high hydrophilic/lipophilic balance value of 15 and low critical micelle concentration (CMC) of 0.014 mM or 0.0018% w/v. The level of polysorbate 80 contained in RESTASIS is several fold above its CMC, and it is expected that some portion of the surfactant will be present in the aqueous phase. This portion of polysorbate 80 is capable of solubilizing both cyclosporine as well as the drug-oil mixture by formation of micelles or microemulsion. Cyclosporine A can be present in the various phases including large and small oil globules, castor oil/polysorbate 80 interface, micellar phase, and solution phase. Further, the distribution of cyclosporine is dependent on Q1/Q2, grades of excipients used, and the process of manufacture.

The significance of the drug distribution in various components or phases of the emulsion and its impact on efficacy and safety of the product is not fully understood. Thermodynamics dictate, however, that the drug localized in different phases may preferentially target partitioning into different ocular tissues depending on their lipophilic or hydrophilic characteristics. For example, the drug in the aqueous phase shows greater affinity towards...
tissues such as the cornea or conjunctiva, and the oil compartment shows greater affinity
towards lipid tissues such as the eyelid margin containing the meibomian glands. Thus, the rate
and extent of distribution in these tissues can be affected by the amount of drug in the different
phases of the emulsion.

5. Changes in physicochemical parameters of emulsion in presence of tears
   (in vitro assessment)

The emulsion characterization methods and results described in previous sections discuss
properties of emulsion drug product. These methods do not address changes that may occur in
emulsion parameters post administration to the ocular surface.

The distribution and disposition of the drug delivered in a complex formulation dosed onto the
surface of the eye is a complex phenomenon that is impacted by the formulation composition
and characteristics plus the disease state of the eye. The ocular surface is supported and
maintained by the tear film, which is composed of 3 components (lipid, aqueous, and mucin). In
normal subjects the osmolality of tear fluid is 300 mOsm. The osmolality of tears is achieved by
the presence of sodium chloride and other salts, which maintains the tonicity of normal tears in
the isotonic range. The tear fluid composition is dependent on the disease state and in dry eye
disease patients the osmolality is higher, in the 330-400 mOsm/L range. When a drop of the
emulsion is administered to the ocular surface, it is expected to interact with the tear fluid and
release the drug on the ocular surface. This interaction and drug release depends on emulsion
characteristics as well as the conditions on the ocular surface.

III. FDA Has Recognized It Lacks Scientific Evidence to Support The In Vitro Approach
     Recommended by The Draft Guidance

FDA’s Draft Guidance proposes that in vitro analyses alone might be accepted to establish that a
proposed generic drug product is bioequivalent to Allergan’s RESTASIS. That proposal is
unsupported by scientific evidence or reasoned explanation.

A. FDA Has Long Recommended In Vivo Testing For Topical Emulsions Based On
   the Available Science

21 C.F.R. § 320.24 sets forth a hierarchy of evidence for measuring bioavailability and
establishing bioequivalence, ranking them “in descending order of accuracy, sensitivity, and
reproducibility.” The regulatory hierarchy consists of (i) in vivo tests in humans or in vitro tests
“correlated with and . . . predictive of human in vivo bioavailability data,” followed by (ii) clinical
trials, then (iii) in vitro tests “that ensure[] human in vivo bioavailability,” and last (iv) “any other

approach deemed adequate by FDA.”

This ordering of evidence reflects the fact that in vivo data from humans (i.e., clinical endpoint data), whether gathered through in vivo tests or more structured clinical trials, is superior to data gathered from in vitro tests and other approaches when determining bioavailability or bioequivalence. Accordingly, when a lower-ranked approach, such as in vitro tests, cannot reliably and scientifically establish bioequivalence, FDA will require that a higher-ranked approach be applied.

When establishing bioequivalence for topical drug products, FDA has long and consistently required in vivo data and concluded that in vitro testing is generally not scientifically reliable or appropriate. In a 1998 draft guidance, the agency categorically stated that “[f]or all topical drug products intended for marketing under an abbreviated application, documentation of in vivo bioequivalence is required under 21 CFR 320.21 (b).”

FDA withdrew the guidance in 2002 for reasons unrelated to this requirement, but FDA has never disavowed that, with narrow, specific exceptions, in vivo testing is required to establish bioequivalence of topical products, and statements by FDA officials in both their professional and personal capacity have confirmed the continued vitality of this essential principle. In April 2004, for example, Robert Lionberger, current Acting Deputy Director for Science at the Office of Generic Drugs, stated that for topical products, “demonstration of bioequivalence requires clinical studies,” except in the case of topical solutions and corticosteroids. He reiterated this position in March 2013, explaining that “FDA often relies on clinical endpoints for bioequivalence” for topical products. Similarly, in December 2012, FDA acknowledged that the agency “has not historically recommended in vitro studies to demonstrate bioequivalence of non-systemically acting semisolid dosage forms.” Instead, FDA has generally recommended in vivo bioequivalence studies with clinical evidence.

39 The order of evidence is: (1) an in vivo test in humans that measures the concentration of the active ingredient/moiety and, when appropriate, its active metabolites, in biological fluid such as blood or plasma as a function of time, or an in vitro test “that has been correlated with and is predictive of human in vivo bioavailability data”; (2) an in vivo test in humans in which the urinary excretion of the active moiety and metabolites are measured as a function of time; (3) an in vivo test in humans in which the appropriate acute pharmacological effect of the active moiety and metabolites as a function of time when no appropriate methods are available under (1) and the effect can be measured with sufficient accuracy, sensitivity, and reproducibility; (4) well-controlled clinical trials that establish the safety and effectiveness of the drug product for measuring bioavailability or appropriate comparative clinical trials for demonstrating bioequivalence; (5) a currently available in vitro test acceptable to FDA that ensures human in vivo bioavailability; and (6) any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence. 21 C.F.R. § 320.24.


endpoints “because formulation differences for locally acting products may affect the availability of a drug at the site of action.”

The agency’s reliance on in vivo data is due in part to the well-recognized difficulty of reliably assessing bioequivalence through in vitro tests because of the low levels of active ingredient that enter biological fluids from topical drug products. As explained in FDA’s 1998 guidance, “measurements in blood, plasma, and/or urine are usually not feasible to document [bioequivalence] because topical dermatologic products generally do not produce measurable concentrations in extra cutaneous biological fluids.” And there are other reasons for relying on in vivo data. In a March 2008 article, for example, Dr. Lionberger wrote that locally acting drugs “often require exploration of alternative bioequivalence methods because plasma concentration profiles of these products are not always appropriate surrogates of pharmacological activity.” He emphasized:

[F]or many locally acting drugs, FDA recommends a bioequivalence study with clinical endpoints . . . [as a] fall-back method because selection of one of the other approaches depends on scientific understanding for a particular drug product, but all drugs have a clinical endpoint used to support their initial approval . . . For many locally acting products that contain suspended drug, in vivo bioequivalence studies are requested because the particle size distribution in suspension cannot be directly compared.

To our knowledge, FDA has never deviated from the position that in vivo data is ordinarily needed to establish the bioequivalence of locally acting topical products.

Given the agency’s position on topical products generally, it follows a fortiori that in vivo evidence is required for topical drug products intended specifically for the eye, which is a more complex, less understood, and a more sensitive organ than the skin. To allow bioequivalence of...
ophthalmic products to be established using less rigorous and reliable scientific evidence would
defy reason and FDA’s mission to protect the public’s health.

FDA has not published a formal policy statement on in vivo data for topical ophthalmic
products, but its officials have consistently recognized in public statements that in vivo data is
needed and in vitro analysis is insufficient to establish bioequivalence for these drugs. In March
2011, for example, Wiley A. Chambers, M.D., Deputy Director of the Center for Drug Evaluation
and Research’s Division of Transplant and Ophthalmology Products, told members of the
American Glaucoma Society that for ophthalmic suspensions, ointments, or emulsions “the
distribution of particles can make a difference, the milling of the particles (i.e., particle size) can
make a difference and therefore the FDA would ask for comparative studies prior to approval of
a generic product.”49 Then, in June 2012, Dr. Chambers, serving in his role as the American
Academy of Ophthalmology’s (“AAO”) expert delegate to the U.S. Pharmacopeia, wrote in the
AAO Journal:

Ophthalmic suspensions, gels, emulsions, ointments, and other nonsoluble
dosage forms present different considerations. Unlike simple solutions, these
products may be affected by altered manufacturing processes such as milling,
particle size distribution, or the order of mixing. Suspensions, gels, emulsions,
and ointments all can be significantly influenced by altered manufacturing
processes even when the active and inactive ingredients are qualitatively and
quantitatively the same. Since 1992, sponsors of proposed generic versions of
post-1962 innovator ophthalmic products have been required to compare their
products to the innovator product in controlled comparative clinical trials and
demonstrate equivalent safety and efficacy using clinical endpoints of efficacy. A
clinical comparison trial is used in this case because unlike solutions, the
 specifications that would be needed [to] judge therapeutic equivalence on a
pure manufacturing basis are not known.50

These statements are consistent with FDA’s stated policy on data required for topical products
more generally.

B. FDA Has Failed to Establish A Scientific Basis for In Vitro Methods to Establish
Bioequivalence of Topical Emulsions.

FDA has admitted that it lacks scientific evidence to support or evaluate in vitro assessments of
physicochemical properties as evidence of bioavailability or bioequivalence of ophthalmic
emulsions. In a notice of available grant funding dated April 27, 2012, FDA sought to sponsor

49 American Glaucoma Society. Questions About Generic Ophthalmic Medications from AGS members, Answered by Wiley Chambers, MD,
FDA Deputy Director for the Division of Transplant and Ophthalmology Products (Mar. 2011), available at

research to address this directly relevant and acknowledged gap in scientific knowledge. FDA stated:

For generic ophthalmic solutions that are qualitatively (Q1) and quantitatively (Q2) the same as the RLD, bioequivalence is considered to be self-evident and a waiver of in vivo study requirements may be requested. For other ophthalmic dosage forms that are Q1 and Q2 the same as the RLD, bioequivalence must be demonstrated as manufacturing differences have the potential to affect ocular bioavailability. . . . Suitable bioequivalence methods are lacking for many generic ophthalmic formulations, including suspensions and emulsions. An investigation of the relationship between various physicochemical properties and their effect on ocular bioavailability will help FDA establish guidelines for the determination of bioequivalence of ophthalmic suspensions and emulsions.51

The application due date was June 23, 2012, and the earliest start date for the requested study was September 2012 (less than one year ago).

During a public meeting on June 21, 2013 – one day after release of the Draft Guidance – Dr. Robert Lionberger of OGD described the equivalence of ophthalmic drugs as an “emerging topic” being considered for FDA’s regulatory science enhancement initiatives. He further stated that the research study evaluating the relationship between various physicochemical properties of ophthalmic drugs and their effect on ocular bioavailability is “ongoing.”52

During the June 21, 2013 meeting, the FDA-commissioned researcher/grantee (Uday Kompella, Ph.D.) presented on the focus and the status of his FDA-sponsored research. Dr. Kompella affirmed the unusual complexity of the ocular environment, and expressed his expert opinion (presumably taking into consideration any information shared by FDA that would be relevant to his research focus and hypothesis) that there currently is a lack of scientific understanding of how physicochemical properties of ophthalmic emulsions affect bioavailability and bioequivalence.53 Far from establishing a new scientific basis for the in vitro testing proposed by the Draft Guidance, Dr. Kompella’s statements and findings to date confirm this approach is extremely premature and of unproven scientific soundness:

➢ The Draft Guidance relies on six physicochemical properties to serve as a crucial indicator of bioequivalence. But Dr. Kompella observed in his presentation that there are “very few to no studies on understanding suspensions and emulsions on the


53 Id. at 281 et seq.
influence of physicochemical properties” and “hardly any literature” on this topic. The available publications are decades old.54

- FDA has repeatedly recognized that particle size variations can significantly affect bioavailability, but as described below (Part VI.B), the Draft Guidance in vitro option cannot be relied upon to detect small structures. Dr. Kompella noted that FDA has not investigated these particles, much less determined their impact on bioequivalence: “With respect to size, less than 1 micron particle[s] have not been clearly investigated, but the current formulations do contain those sizes, including the emulsion that are about 200 nanometers in size.” “And then what is the influence of those sizes on bioequivalence[? T]hat’s not known.” With respect to particle size distribution, he explained, it is possible for two formulations to have the same mean size, but different distribution patterns. This leaves the unanswered question: “What does that mean to bioavailability?”55

- Dr. Kompella noted that “[a]ny difference in residence time might cause difference in bioavailability.” This is significant because the Draft Guidance-approved release testing is generally conducted over several hours, while the time duration on the ocular surface is usually limited to a few minutes.

- Dr. Kompella affirmed that his FDA-sponsored research is ongoing. He described a step-wise progression that currently involves in vitro studies using animal tissues (ex vivo eyeballs shipped from slaughterhouses), current “screening” studies in rats and eventually planned further studies in rabbits. Even when he presented a model under development, Dr. Kompella clarified that it ultimately will be necessary to validate the model with in vivo results. In other words, the research is nowhere near completed, and there is no basis to conclude at this time that current findings will ever be validated against in vivo human testing, as they must be.

In short, FDA recognized less than sixteen months ago that the scientific foundation for reliance on in vitro testing to assess bioequivalence of emulsions is “lacking.” Nothing has changed; the study-in-progress that FDA commissioned to fill that void has yielded more questions than answers. Yet the agency has inexplicably proposed abandoning its long-held position grounded in science and adopting new criteria for bioequivalence testing unsupported by science. This is a paradigmatic case of arbitrary and capricious agency action.

54 Id. at 294.

55 Id. at 295-296. One micron is also expressed as 1000 nanometers (nm). RESTASIS includes a substantial proportion of globules less than 1/10th that size – i.e., smaller than 100 nm.
IV Scientific Evidence Demonstrates FDA’s Draft Guidance Would Permit Non-Bioequivalent Products To Be Deemed Bioequivalent.

FDA’s failure to provide a scientific basis for the in vitro option recommended in the Draft Guidance is reason enough to revise the Draft Guidance. But the available science is not merely silent or neutral on this issue. FDA must confront substantial scientific evidence that undermines its unsupported assumption that bioequivalence can be established by the test proposed in the Draft Guidance. Based on preclinical studies, Allergan has established that the in vitro criteria proposed in the Draft Guidance are inadequate to assess bioavailability or ensure bioequivalence of a proposed generic formulation for RESTASIS. Allergan has identified significant analytical data that further demonstrate that cyclosporine formulations can be Q1 and Q2 and meet the physicochemical parameters identified in the Draft Guidance, yet in fact be highly dissimilar in ways that are material to bioavailability and bioequivalence.

A. Under the In Vitro Option, Drugs Differing In Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy Would Be Considered Bioequivalent.

FDA has disclosed no scientific evidence to support its assumption that the in vitro testing proposed by the Draft Guidance is capable of validly measuring bioequivalence. To the contrary, the only hard evidence of which Allergan is aware supports the opposite conclusion: the Draft Guidance would permit non-bioequivalent products to be erroneously deemed bioequivalent.

To evaluate FDA’s Draft Guidance, Allergan manufactured several product formulations that closely resemble RESTASIS and would satisfy the terms of the Draft Guidance. Allergan’s experimental formulations were Q1/Q2 with respect to ingredients and comparable with respect to the six physicochemical characteristics identified in the Draft Guidance (globule size, pH, viscosity, zeta potential, surface tension, and osmolality). Despite these apparent similarities, analytical and animal assessments of these formulations reveal important product differences and demonstrate that the Draft Guidance can inaccurately identify non-bioequivalent products as bioequivalent to RESTASIS.

The Allergan data are being submitted to NDA 50-790, due to the trade secret and confidential commercial information revealed therein. It is incumbent on FDA to study these data, as they reveal that formulations satisfying the Draft Guidance criteria may in fact exhibit differences in in vivo pharmacokinetics and pharmacodynamics (key determinants of bioequivalence) as well as differences in efficacy and safety.

In summary, the data show:

---

56 Allergan was unable to perform release tests on these experimental formulations, however, as no in vitro release test exists for RESTASIS, and none has been established or validated for an ophthalmic formulation.
• More sophisticated analytical evaluation of the test emulsions demonstrated that certain of the formulations differed measurably from RESTASIS with respect to drug distribution in the emulsion.\(^{57}\)

• Pharmacokinetic studies in rabbits and dogs (using defined protocols, highly precise dose administration tools, and quality practices that Allergan has followed consistently for years) revealed the following about the test formulations:
  
  o Maximum concentration (\(C_{\text{max}}\)) levels of the test formulations were from 0.95- to 9.03-fold the levels measured with RESTASIS;
  
  o Area under the curve (AUC) exposure totals ranged from 0.78- to 3.33-fold the levels measured with RESTASIS; and
  
  o Time to maximum concentration (\(T_{\text{max}}\)) periods were equal to or up to 5.5 hours faster than provided by RESTASIS.\(^{58}\)

• Certain formulations in animal pharmacokinetic studies achieved higher cyclosporine concentrations in tears, with a wider range of variability as compared to RESTASIS. These higher cyclosporine tear concentrations are thought to contribute to increased severity of ocular discomfort and conjunctival hyperemia that was observed in test animals as compared to RESTASIS.

Together these data confirm that (1) changes in the manufacturing process do alter cyclosporine ocular tissue pharmacokinetics; and (2) bioequivalence to RESTASIS in humans is unlikely to be ensured by conformance with the in vitro criteria proposed by FDA. These changes in ocular tissue pharmacokinetics likely have consequences on the in vivo performance of an emulsion that meets Q1/Q2 criteria and the physicochemical parameter measures set out in the Draft Guidance, such that it would not be therapeutically equivalent to RESTASIS and potentially could represent a threat to patient safety or effectiveness by delivering concentrations of cyclosporine that differ dramatically from that delivered by RESTASIS.

B. The In Vitro Approach Cannot Reliably Measure Drug Distribution Throughout the Emulsion—Which Is Essential for Bioequivalence

Drug distribution and globule size can have a substantial effect on bioavailability. In vitro testing cannot ensure accurate assessment of drug distribution because common methods are incapable of detecting small globules that contain a substantial portion of the drug in RESTASIS.

\(^{57}\) See Section IV.B.1 below.

\(^{58}\) Although the eyedrop is cleared in minutes (i.e., 97% of the drug substance is cleared, leaving 3% for absorption), the absorbed drug will equilibrate across tissues over time. The time to maximum concentration in a given tissue is a function of the time to achieve a concentration equilibrium between the tear film and tissues.
That deficiency is an independent reason why the in vitro option proposed in the Draft Guidance cannot be relied upon to demonstrate bioequivalence.

As previously described, RESTASIS is an oil-in-water emulsion comprised of multiple phases in which drug exists in free form or in globules of different sizes. For example, the oil phase contains large and small globules, while the aqueous and microemulsion phases include free drug and drug in very small globules (in addition to drug in solution and associated with surfactant and viscosity agents). As FDA has recognized for other drugs, “particle size can have a significant effect on dissolution rates, bioavailability and/or stability.”

In the context of RESTASIS, Allergan has proprietary nonclinical (rabbit) data showing that drug from different emulsion phases is bioavailable at different rates and extents in different ocular tissues. Thermodynamics dictate that the drug in globules of different types and sizes from different phases preferentially targets different ocular tissues depending on the globules’ lipophilic or hydrophilic characteristics (e.g., drug in the aqueous phase may show greater affinity for the cornea or conjunctiva, while drug in the oil phase may preferentially seek tissues such as the eyelid margin and meibomian glands). The rate and extent of drug distribution into each tissue also may be affected by the phase of emulsion from which the drug originated.

Because it is not definitively known which ocular tissue(s), combination(s) of tissues, or minimum number of tissue(s) must receive what minimum or maximum amounts of cyclosporine to ensure safe and therapeutic effects, demonstrating an equivalent drug distribution across phases and globules is critical to showing that any proposed generic is bioequivalent to RESTASIS. On this critical point, the Draft Guidance acknowledges the importance of globule size by requiring certain comparative analysis of globule size distribution. However, it is widely accepted that the measurement of globule size and globule size distribution of emulsions is very dependent on the methodology used for measurement. There is no standardized, agreed upon methodology for the measurement of globule size or distribution for ophthalmic emulsions, so reliance on such techniques is simply inadequate to demonstrate bioequivalence. The primary reason for this inadequacy is complex but simply stated: commonly used methods do not reliably detect the smallest components of the drug (submicron components less than 100 nm), let alone micellar structures in that range, but those components significantly affect bioavailability.

1. **Globule Size Distribution Cannot Measure Drug in All Phases of the Emulsion, Including Drug in Critical Submicron Globules**

Globule size distribution is a bulk characterization technique, i.e., it is used to characterize the emulsion formulation as a single entity. It does not and cannot characterize distribution of the drug within the various phases and components of the emulsion. Proprietary Allergan

---

experiments show that a substantial fraction of drug in RESTASIS is distributed in submicron globules less than 100 nm in the aqueous and microemulsion phases (clear phases) of RESTASIS (these phases include free drug, micelles, and small globules). Allergan also has proprietary nonclinical data showing that the amount of drug in these phases directly impacts drug availability at the ocular sites of action. But common globule size distribution techniques do not reliably measure globules this small in size.

In particular, while there is no universal technique for measuring globule size distribution, for submicron emulsions, the most common techniques are Static Light Scattering (SLS) (also known as Laser Light Diffraction) and Dynamic Light Scattering (DLS) (also known as Photon Correlation Spectroscopy). These techniques deduce distribution of globule sizes based on measurements of light scattered by globules dispersed in a beam of light.

The instruments used for these measurements have limitations that constrain or prevent the measurement of large angles of light scattering associated with submicron globules of the smallest sizes in the clear phases of RESTASIS. The instruments are also limited because larger globules can obscure smaller globules, rendering them undetectable. This is evidenced by globule size distribution analyses Allergan performed for multiple samples from the same lot of RESTASIS using a common light scattering method. The analyses show a lack of unity of the globule size distribution curves for these samples with respect to globules less than 100 nm.

This defect in FDA’s proposed in vitro option is not a mere theoretical concern. It is confirmed by hard evidence revealing that emulsions can satisfy the Draft Guidance yet differ markedly in drug distribution patterns. Allergan has proprietary evidence that experimental formulations that are Q1/Q2 similar to RESTASIS and adhere to all six physicochemical parameters in the Draft Guidance (including with regard to globule size distribution using common light scattering techniques) are nonetheless dissimilar to RESTASIS with respect to the distribution of cyclosporine in submicron globules less than 100 nm. Critically, the experiments show that several of these formulations have substantially different quantities of active drug substance in the phases of emulsion containing the smallest (submicron) globules compared to RESTASIS. In addition, using a more precise methodology for measuring globule size distribution, Allergan found further evidence these experimental formulations are, in fact, highly divergent in drug distribution compared to RESTASIS.

As explained above, drug distributed in different globules and phases of the emulsion is bioavailable at different rates and extents in different ocular tissues. These findings are thus compelling evidence that the active drug in these formulations may be absorbed differently in the ocular tissues and exhibit divergent bioavailability – and, thus, that the Draft Guidance’s in vitro approach cannot ensure bioequivalence. This conclusion is reinforced by the human corneal epithelial and preclinical data described above that plainly show differences in tissue absorption and/or poorer tolerability associated with the formulations.60

60 See Section IV.A below.
2. Additional Limitations of Globule Size Distribution and Viscosity Measurements May Cause Dissimilar Products to Appear the Same

Beyond their inability to reliably measure submicron globules, common techniques for determining globule size distribution have other significant limitations for emulsions like RESTASIS, including the following:

- For emulsions that have a bimodal distribution (one that consists of two peaks, instead of one), common techniques may detect only one of the peaks in the distribution.

- As shown by Allergan in internal experiments, globule size distributions can appear similar or dissimilar between the same samples, depending on use of differing sampling techniques (e.g., selection of sample volume, stirring speed, sonication), measurement conditions, or instrument settings (even when the techniques, conditions, or settings selected are within acceptable ranges defined by method parameters).

- Variations among instruments and associated algorithms, as well as complexities of fitting statistical or mathematical distributions to relevant data, can cause diverse distributions to be produced by different instruments for the same sample. Globule size analyses performed by Allergan using three instruments on samples from five lots of RESTASIS bear this out, showing in some cases 2-3 fold differences in D50 and SPAN for the same sample using different instruments. Similarly, certain of the test emulsions created by Allergan have D50 and SPAN values similar to RESTASIS when measured using one instrument, yet have dissimilar values to those for RESTASIS when measured using another instrument.

The potential for these issues to create inaccurate or unreliable globule size distribution measurements is particularly significant for cyclosporine emulsions, because common methods like microscopy are unable to confirm the true globule sizes within the emulsions due to their viscous nature. Even apart from the other reasons in vitro data alone cannot demonstrate bioequivalence as to RESTASIS, measuring globule size distribution is unreliable and cannot serve as even a partial surrogate for bioavailability without an accepted methodology for measuring globule size distributions that is sufficiently robust to ensure that variations in sampling technique, measurement conditions, and instrument parameters cannot result in a showing of similarity for emulsions that are dissimilar. Allergan knows of no such method.

Besides globule distribution, viscosity measurements may also lack value in determining physicochemical equivalence of cyclosporine ophthalmic emulsion formulations if assessed at a

---

single point of shear. The Draft Guidance does not specify any method for viscosity measurements and does not prohibit a single-point measurement. However, while single-point viscosity measurements are used as a quality control parameter, they are not adequate in any assessment of bioequivalence.

RESTASIS contains carbomer copolymer type A, which is a shear-thinning polymer. As such, its viscosity decreases with increasing rates of shear. Shear-thinning is a desirable property for an ophthalmic emulsion, as it permits the emulsion to have high viscosity and, thus, stability when at rest during storage, but to have low viscosity when squeezed, which aids administration to the ocular surface and drug release from oil globules there. Decreased viscosity upon administration also helps prevent vision blurring.

Because viscosity for cyclosporine ophthalmic emulsion is a function of applied shear (i.e., the product exhibits non-Newtonian rheological characteristics), a single point viscosity measurement would not inform the functional viscosity and rheological properties of the emulsion post-ocular administration. As with globule size distribution, even a valid in vitro assessment of the rheological properties of the emulsion would not address the fundamental reasons why in vivo bioequivalence must be demonstrated through comparative clinical studies. But to be valid, a viscosity assessment, especially for such a non-Newtonian fluid, must incorporate the full viscosity profile as a function of applied shear, and not rely on just a single-point viscosity measurement. Any dissimilarity between emulsions at any level(s) of shear would have high potential to impact drug bioavailability, given the impact of viscosity on drug release at the ocular surface.

3. Additional Testing, Including In Vivo Testing, Is Needed to Address the Shortcomings of the Draft Guidance’s In Vitro Option

In light of the above-discussed limitations and failures of physicochemical testing to ensure equal distribution of drug substance across globules of different sizes, including those less than 100 nm, it is clear that testing beyond what the Draft Guidance proposes is required. Specifically, applicants must devise and demonstrate the validity of tests beyond common, existing techniques for measuring globule size distribution to comprehensively assess and ensure equivalence of drug distribution in all phases of the emulsion, including in submicron globules less than 100 nm (including validating the results by demonstrating that variations in sampling techniques, measurement conditions, or instrument settings do not lead to variations in results). Moreover, applicants must also perform viscosity testing that assesses the product’s full viscosity profile as a function of applied shear, rather than merely measure viscosity at a single point.

Even if additional testing in these regards is developed and successfully performed, as previously noted, there is presently no science establishing an in vitro-in vivo correlation for the Draft Guidance’s physicochemical parameters; there is also presently no valid scientific basis on which to conclude that these parameters comprise the totality of factors relevant to
bioavailability and bioequivalence. Thus, based on current science, bioequivalence can be validly demonstrated only using in vivo (in addition to, and not in lieu of, in vitro) methods.

C. There Is No In Vitro Drug Release Methodology Established for RESTASIS or to Characterize Ophthalmic Emulsions

One of the mandatory elements of the Draft Guidance’s in vitro option is comparative in vitro drug release testing of both RESTASIS and a proposed generic drug formulation. This presents a major problem: No in vitro release test exists for RESTASIS, and none has been established or validated for an ophthalmic formulation. Indeed, FDA has acknowledged the difficulties in developing suitable drug release tests for ophthalmic products, in various workshops on In Vitro/Dissolution testing of Novel/special dosage forms. For example, in the summary report of a workshop co-sponsored by FDA and the International Pharmaceutical Federation, ophthalmic dosage forms are listed as “requiring more work before an in-vitro drug release method can be recommended.”

For a highly complex dosage form, such as RESTASIS emulsion, use of an in vitro release method becomes an even greater challenge because of the multiple phases and components of the emulsion (each with varying properties) in which drug exists and from which it must be released. The challenge is greater still given the complexity of dry eye disease and the impacts it has on the ocular surface parameters. These considerations make it extraordinarily difficult to develop an in vitro release method to measure accurately the release of an emulsion like RESTASIS in the ocular environment.

If one were required to design such a test, the following factors, at a minimum, would have to be minimally modeled into the test to accurately consider a complex product such as RESTASIS:

1. Short duration/residence time available for drug release (< 5 min after application to the eye).
2. Mimic tear composition in target patient population (dry eye patients) and the impact this composition has on the dynamic changes to emulsion characteristics, such as viscosity changes and emulsion breakup.
3. Simulate the impact of (a) tear dilution and (b) turnover rate on drug availability to target tissues. The dilution effect of increased tear production from even the application of the emulsion vehicle, and convective-diffusion transport processes due to the fluid flow from nasolacrimal drainage, are specific considerations that must be addressed.
4. Effects of shear from blinking on the emulsion rheology as well as the transport processes.

---

5. Differential drug release and tissue uptake, considering both (a) multiple target tissues expected to be involved in the treatment of dry eye, and (b) the fact that tissue uptake can be through diffusion or direct partitioning from the emulsion phase.

In addition to incorporating the above phenomena into an in vitro release test, any such test would need to be validated for reliability and to predict bioequivalence through in vitro-in vivo correlation per established practices. Unless the test can be reliably established to reflect actual conditions of drug administration, there would be no basis to use it as a predictor of performance in the intended physiological system.

Notwithstanding these challenges, changes in emulsion characteristics after mixing with tear fluid were evaluated experimentally in vitro for RESTASIS and experimental emulsions that satisfied the Q1/Q2 and physicochemical criteria described in the Draft Guidance. Although it is not an adequate medium (for reasons just described), saline solution (0.9% NaCl) was used to represent tear fluid for healthy subjects. The changes in globule size distribution and viscosity after 1:1 dilution of emulsion with saline were measured using DLS techniques and a rheometer respectively. It was observed that, for RESTASIS after dilution with saline, a larger portion of the drug is present in the aqueous phase. For emulsions with different manufacturing process, however, the increase in the aqueous portion of drug post-dilution was not identical to RESTASIS. In fact, for one emulsion, almost no increase in the aqueous portion of the drug was observed. Thus, it would be expected that emulsion, which met the Q1/Q2 and globule size distribution criteria, would not show similar performance in in vivo.

D. Current Drug Release Test Methods for Disperse Systems Are Not Designed To Capture Key Characteristics of RESTASIS

Common methods proposed in the literature for testing in vitro drug release for disperse systems can be grouped into three major categories: sample and separate technique, membrane diffusion technique (dialysis sac), and continuous flow-through technique.63

a) Sample and separate technique: This method is recommended for drug release testing for oral suspensions for systemic use. In general, the rotating paddle method using an aqueous dissolution medium is the recommended method for dissolution testing of suspensions. Suspension samples are delivered to the bottom of the dissolution vessels with agitation rate selected based on viscosity of the suspensions.62 The drug released in the aqueous medium is measured by suitable analytical techniques. This method is not applicable to RESTASIS as the emulsion would disperse throughout the aqueous dissolution medium making it impossible to separate the dissolved or released drug. Techniques such as filtration or centrifugation would not be applicable to separate the dissolved drug phase as the micellar portion of the drug will be present in the clear portion obtained. Drug release rate or extent cannot be accurately determined for a submicron emulsion such as RESTASIS with this technique.

b) Membrane diffusion technique (dialysis sac): The dialysis sac method or the rotating dialysis cell model is mostly preferred for disperse systems because the dissolution/release media and the particles are already physically separated by a membrane, and there is no need for extra separation before the sample measurement, or for the retention of specimens in the system. In this technique, the sample for drug release testing is filled into a dialysis bag, which is then sealed and placed in a dissolution apparatus containing a suitable media. Samples of the media are analyzed to measure drug release. This technique has been used widely in ophthalmic drug delivery research for novel dosage forms. Selection of a suitable dialysis membrane and dissolution media is a critical factor in developing a meaningful drug release test method. For a cyclosporine ophthalmic emulsion, this method has limitations including:

I. Due to similar molecular weights of CsA (~1200) and polysorbate 80 (~1300), selection of a dialysis membrane that allows diffusion of CsA but not of polysorbate 80 is nearly impossible. In this case, drug release from the micellar component cannot be measured.

II. This method does not take into account the changes in the emulsion due to dilution with tears or the rapid loss of drug due to pre-corneal clearance.

III. Release testing is generally conducted over several hours, while on the ocular surface the time duration is usually limited to a few minutes.

c) Continuous flow-through technique: This technique utilizes USP 4 dissolution apparatus to measure dissolution and drug release from a disperse dosage form into a suitable media. For emulsions such as RESTASIS, this technique suffers from similar limitations described for the previous two techniques. These include:

I. Difficulty in separating CsA release in aqueous media from the small globules (<100nm) and micellar component.

II. Rapid pre-corneal clearance is not considered.

III. Effect of dilution of emulsion with tear fluid is not considered.

Due to these limitations, these techniques typically used for disperse systems are not suitable for drug release testing from RESTASIS or proposed generics referring to RESTASIS.

E. In Vitro Drug Release Testing Cannot Simulate the Complex Drug Release and Delivery to Receiving Compartments (Ocular Tissues)

For most drug release testing applications, the drug delivery is to a single compartment. In the case of oral delivery, for example, the drug release compartment is the gastrointestinal fluid. For parenteral delivery, the compartment is the site of administration. Simulated biological
fluids have been designed to mimic these delivery compartments to measure delivery rates and performance of these dosage forms. For ophthalmic delivery, however, the drug release is not limited to a single compartment, as an administered drop can quickly spread to all the ocular surface tissues. Furthermore, delivery to multiple target tissues is believed to be an important feature of cyclosporine’s therapeutic effect. Simply measuring drug release into simulated tear fluid is therefore not sufficient.

Currently, it is not feasible to design a receiving compartment that simulates all the tissues to which the drug is delivered, such as conjunctiva, cornea, lacrimal gland, lymph nodes, eyelid margin, etc. Hence even if a drug release testing method were proposed, it could not predict the actual performance of a generic emulsion in comparison to RESTASIS in the relevant administration environment and at all the relevant tissue compartments.

In short, the complexity of the disease and its ocular distribution, the very short time that the drug is in contact with the target tissues, and the complex multi-phase formulation mean that no valid in vitro test that would be predictive of clinical performance has been created or can be created given the current state of scientific understanding.

V. A Clinical Endpoint Study Is Required Because Product-Specific Factors and the Precise Mechanism of Action of RESTASIS are Unknown to the Scientific Community

FDA suggested in the Draft Guidance that it discounted the need for in vivo clinical studies because the effect of RESTASIS in its clinical studies was “modest.” As discussed in Section II.B, in fact, the studies of RESTASIS reached a high bar set by FDA and confirmed the importance of this innovative drug product to patients suffering from the most severe forms of dry eye disease. Several different clinical trial designs may be available to a generic manufacturer to compare its product to RESTASIS, and there is room to select from the most efficient pathway that satisfies the bioequivalence standards. More fundamentally, even if it were true, which it is not, that it would be impossible as a practical matter for an ANDA applicant to conduct comparative clinical studies to demonstrate equivalent safety and effectiveness, that would not justify the in vitro approach proposed by the Draft Guidance. The legal requirement of bioequivalence may be difficult to satisfy in some circumstances, but that requirement applies across the board. Likewise, “scientifically valid” methods of demonstrating bioequivalence in vitro may not yet have been developed in certain contexts, but that does not mean that scientifically invalid methods may be used instead. The ANDA applicant bears the burden of satisfying the legal requirements for approval. Where the applicant does not satisfy those


66 See Letter from Janet Woodcock, M.D., FDA, to Philip J. Honerkamp, Jazz Pharmaceuticals, Inc., re: Docket No. FDA-2012-P-0499 (November 13, 2012) [hereinafter Jazz Petition Response] (“FDA...accepts alternative data and methods proposed by individual ANDA applicants as long as that data meets the statutory requirements for approval”).

requirements, the agency has no authority to lower the bar out of a desire to make it easier to obtain approval.

The Draft Guidance would permit a bioequivalence determination to be based upon in vitro parameters that bear an untested and presently unknown relationship to bioavailability, safety, and therapeutic effect of the underlying product. FDA’s proposed in vitro method necessarily assumes that generic applicants and FDA have: (i) accurately identified product-specific factors (e.g., globular size composition and distribution in multiple phases, both in the vial and after administration to the eye), and (ii) scientifically understood the product’s mechanism of action (including differential interaction with different ocular tissues after administration to the eye). Without this prerequisite understanding, it is impossible for FDA to quantify and compare rates and extent of absorption in accordance with applicable bioequivalence standards.

As discussed above, however, FDA lacks fundamental information to understand how specific physicochemical parameters of an emulsion impact product availability in the eye. Further, although animal data demonstrate that there is differential uptake by different tissues depending on globule sizes and other factors, there has not been identification of the precise ways RESTASIS interacts with individual ocular tissues, which would be necessary to evaluate appropriate rates and extent of absorption.

Fundamentally, and as a matter of common sense, to define bioavailability and bioequivalence criteria, one must have a reasoned basis for deciding where to look, knowledge of what to look for, and reliable tools to measure and compare parameters. Here, there are major gaps impacting all three areas.

FDA has acknowledged that the selection of a bioequivalence method for a locally acting drug necessarily must be based on what is known about product-specific factors and its mechanism of action. As Dr. Lionberger observed in 2008, all drugs have a clinical endpoint, and that is the only valid tool when other approaches have not been proven:

[F]or many locally acting drugs, FDA recommends a bioequivalence study with clinical endpoint. It has become the fall-back method because selection of one of the other approaches depends on scientific understanding for a particular drug product, but all drugs have a clinical endpoint used to support their initial approval.[68]

---

68 Lionberger R.A. FDA critical path initiatives: opportunities for generic drug development. AAPS J. 2008;10(1):103-109 (emphasis added); see also Jazz Petition Response, supra note 66, at 9 (“[A] determination of the appropriate bioequivalence methodology must be supported by scientific evidence”); Id. at 12 (“[21 C.F.R. §] 320.24(a) provides that “[t]he selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. This regulation requires applicants to ‘conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section.’”).
Dr. Lionberger’s observation is entirely in keeping with FDA’s regulatory methodology, which specifically recognizes that different types of drug products demand different types of bioequivalence testing. For example, 21 C.F.R. § 320.24(a) requires that “[t]he method used [to meet bioequivalence-testing requirements] must be capable of . . . establishing bioequivalence . . . for the product being tested.” In the case of RESTASIS, the foregoing shows that in vitro methods are not presently capable of establishing bioequivalence. Section 320.24(a) additionally requires that “[a]pplicants shall conduct . . . bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in” section 320.24(b). Section 320.24(b), in turn, provides that, where other methods are not available, “appropriately designed comparative clinical trials[ ] for purposes of demonstrating bioequivalence” are a suitable way of “demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally . . . [to] the . . . eye.”

VI. An In Vivo Approach to Bioequivalence is Required as a Matter of Public Health

The methods FDA permits manufacturers to rely on to establish bioequivalence must be rooted in, and not defined ahead of or contrary to, available knowledge and sound science. Two paramount reasons are the public health and FDA’s commitment to ensure that “providers and the public alike never have to question their confidence in high quality generic products.”

Bioequivalence is the cornerstone of FDA’s generic drug approval process and public confidence in the safety and effectiveness of generic drugs. The validity of a finding of bioequivalence for any proposed generic drug is, therefore, essential.

As explained in this comment, bioequivalence between any generic cyclosporine emulsion and RESTASIS can be validly ascertained only through in vivo clinical studies in humans. Getting the bioequivalence determination right is critical for several reasons. First, a lack of bioequivalence could mean a generic is sub-potent. In that event, a patient’s dry eye disease may go untreated and continue to progress, leading to scarring and vision loss. Based on controlled clinical trials of RESTASIS, three to six months of treatment (depending on the endpoint) are needed before dry eye symptoms are significantly improved. Thus, treatment with a sub-potent generic version could expose patients to months of poorly effective therapy before the sub-potency is detected, risking further deterioration of patients’ already serious disease condition. The risks of sub-potency are exacerbated in many cases because a significant number of patients who suffer from dry eye disease are especially vulnerable to further ophthalmic stressors. These vulnerable patients tend to be elderly, and maintaining their sight plays a particularly critical role in their ability to remain independent.

69 21 C.F.R. § 320.24(b)(iv).

In addition, the most common reason for discontinuation of RESTASIS among patients generally in clinical trials and in clinical practice has been the burning/stinging associated with applying the product to the eye. If a generic is not equivalent to RESTASIS, it could be less well tolerated by patients (i.e., more likely to burn/sting on contact) and, as a result, patients would be less likely to adhere to their treatment regimen. This could also cause ineffective treatment of the disease, with related clinical harms. A reduced frequency of RESTASIS dosing has been associated with poorer patient satisfaction with their treatment. Thus, ensuring that any generic emulsion is truly bioequivalent to RESTASIS is critical to patient compliance, effective disease treatment, and avoiding patient harms that result from disease progression associated with ineffective treatment.

Ensuring bioequivalence of any generic ophthalmic emulsion is, moreover, important to the public more broadly, and to FDA’s commitment to maintain the public’s confidence in generic drugs categorically. Several generic ophthalmic drugs have, post-approval, unexpectedly shown less efficacy than their reference drug and/or clear drug-related toxicity. In addition to the harms that result for specific patients, these cases imperil the public’s confidence in generic drugs generally. One example is generic latanoprost suspension, which has been shown to be significantly less efficacious at reducing intra-ocular pressure (IOP) in glaucoma patients versus branded latanoprost (Xalatan®); in addition, generic latanoprost has been associated with more adverse events and was positively linked to a published case of corneal epithelial disorder. Additional examples of past generic cases of inequivalence include diclofenac causing corneal melts, ciprofloxacin sub-optimal drug concentration, prednisolone acetate, and ketorolac and timolol gel forming solution. Additionally, analytical testing of generic latanoprost, dorzolamide-timolol, and bimatoprost samples found variations in product strength, the extent of product stability, and particle size that are outside the acceptable ranges, although it is

71 Trattler W., Katsev D., Kerney D. Self-reported compliance with topical cyclosporine emulsion 0.05% and onset of the effects of increased tear production as assessed through patient surveys. Clin Ther. 2006;28:1848-1856.


unclear if these problems can account for all of the documented clinical differences in these products.77

As these examples illustrate, differences in a generic product could pose a significant hazard to the ophthalmic health of patients and could cause patients and prescribers to be more reluctant to use generic products. As Commissioner Hamburg remarked earlier this year to the Generic Pharmaceutical Manufacturers Association, much “hard work” is needed to “convince a skeptical public that a generic drug [i]s a therapeutic equivalent of a brand name drug”; additionally, FDA and industry’s “task is ensuring that [generic] medications that ... millions of Americans take every day are safe, effective and of high quality.”78 These goals can only be achieved by approving generic drugs on the basis of bioequivalence methods that are valid, supported by, and consistent with existing science. In the case of cyclosporine ophthalmic emulsions, the appropriate method based on existing science is the use of clinical endpoints for in vivo bioequivalence testing, as those endpoints have been well established, including through the clinical studies supporting RESTASIS’ approval. By contrast, as detailed in this comment, in vitro methods not only lack scientific support, but are demonstrably inadequate based on available data.

VII. The Draft Guidance Is Inconsistent With The FDCA And FDA Regulations And Contrary To The APA Requirement Of Reasoned Decisionmaking

If FDA were to find that a generic drug is bioequivalent to RESTASIS without requiring in vivo testing, as the Draft Guidance proposes, FDA’s action would violate the FDCA, its implementing regulations, and basic principles of administrative law.

A. The In Vitro Approach Proposed in the Draft Guidance Violates the FDCA

The FDCA contains two specific provisions governing the approval of generic versions of drugs that, like RESTASIS, are “not intended to be absorbed into the bloodstream.” 21 U.S.C. § 355(j)(8)(A)(ii) and (j)(8)(C). The Draft Guidance does not cite either of them. Instead, it invokes FDA’s regulation stating that FDA may permit alternative approaches of establishing bioequivalence as the agency “deem[s] adequate.” 21 C.F.R. § 320.24(b)(6). That regulation, however, cannot be used to overcome the on-point statutory provisions constraining FDA’s authority and requiring a specific showing for drugs not intended to be absorbed into the bloodstream. With respect to that class of drugs, the statute authorizes only two alternate approaches for assessing bioavailability and testing bioequivalence, and the Draft Guidance does not satisfy either of them.


78  Id.
First, section 355(j)(8)(A)(ii) provides: “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.” 21 U.S.C. § 355(j)(8)(A)(ii) (emphasis added). This provision recognizes that, unlike a drug that works by circulating through the blood, the bioavailability of a locally-acting drug can be determined only by measuring how quickly and effectively its active ingredient reaches the tissues that the drug is designed to treat. The Draft Guidance does not invoke this authority. It does not even purport to address whether in vitro testing is capable of producing “scientifically valid measurements” of bioavailability as required by this provision. Nor does it comment on the reliability of in vitro measurements of bioavailability “at the site of drug action.” Instead, as described above, the Guidance relies on six physicochemical parameters that have an unknown and untested relationship to the rate and extent to which the active drug in RESTASIS reaches the multiple ocular tissues that it treats.

Second, section 355(j)(8)(C) provides: “For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.” Id. § 355(j)(8)(C) (emphasis added). But the Draft Guidance does not comply with this provision either. Nothing in the Draft Guidance identifies, much less provides a reasoned explanation for adopting, any alternative scientifically valid method that is expected to detect significant differences in safety and therapeutic effect.

The in vitro option proposed by the Draft Guidance violates the FDCA because it satisfies neither of these alternative standards for demonstrating bioequivalence. As discussed above, the simple truth is that there are no “scientifically valid” in vitro measurements or methods of analysis to reliably assess the bioavailability or bioequivalence of a proposed generic formulation of RESTASIS. The criteria suggested by the Draft Guidance are plainly inadequate. Experimental testing shows that formulations satisfying all of the factors set forth in the Draft Guidance are absorbed differently by the multiple ocular tissues and exhibit differing bioavailability. Absent a scientifically valid in vitro method to measure bioavailability or to establish bioequivalence, there is no shortcut possible and comparative clinical testing is required to show equivalent safety and effect based on clinical endpoints.

More fundamentally, FDA has no authority to apply the in vitro approach recommended in the Draft Guidance without undertaking notice-and-comment rulemaking. Section 355(j)(8)(C) prohibits FDA from applying “alternative” procedures through ad hoc decisionmaking. Instead, because relying on alternative methods to show bioequivalence (where bioavailability cannot be measured directly) can have significant consequences for human health and welfare, Congress required the Secretary to “establish” any such alternative testing procedures before those measurements may be applied to an application in any particular case. “Establish” connotes formality, permanence, and binding future effect: Black’s Law Dictionary defines it to mean, “To
settle, make, or fix firmly; to enact permanently.” *Id.* (9th ed. 2009). The statute thus contemplates a process that is “prospective in operation and general in scope” and that will achieve even-handed uniformity by giving “interested parties . . . advance notice of the standards to which they will be expected to conform.” *Trans-Pacific Freight Conference of Japan/Korea v. Federal Maritime Comm’n*, 650 F.2d 1235, 1244–45 (D.C. Cir. 1980); see also *Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1020 (D.C. Cir. 2000) (“[o]nly ‘legislative rules’ have the force and effect of law”). In contrast, the Draft Guidance does “not operate to bind the FDA or the public” and cannot be said to “establish” anything. Indeed, the D.C. Circuit has explained that statutory provisions providing that “[t]he [HHS] Secretary shall establish” certain requirements should be understood to “clearly and explicitly impose a rulemaking requirement”—even though the provisions at issue did not expressly refer to rulemaking. *Gray Panthers Advocacy Committee v. Sullivan*, 936 F.2d 1284, 1291 (D.C. Cir. 1991) (quoting 42 U.S.C. §§ 1395i–3(f)(2)(a)(i)–(iii), 1396r(f)(2)(a)(i)–(iii)). The duty to “establish” an alternative method can no more be satisfied by nonbinding draft guidance than by the ad hoc application of that guidance to individual ANDAs. Rulemaking, not case-by-case adjudication, is the proper means of establishing new, forward-looking standards. See *Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 221 (1988) (Scalia, J., concurring) (“[a]djudication deals with what the law was; rulemaking deals with what the law will be”); *Bergerco Canada v. U.S. Treasury Dep’t*, 129 F.3d 189, 192–93 (D.C. Cir. 1997) (treating Justice Scalia’s concurring opinion as substantially authoritative).

In any event, even if it were permissible for FDA to avoid notice-and-comment rulemaking, the Draft Guidance does not purport to establish any scientifically valid “methods,” as § 355(j)(8)(C) requires. At most, the Draft Guidance identifies certain parameters that it recommends be tested in vitro. In vitro testing, however, is not a “method” as the term is used in the statute. “Methods” are specific scientific processes. See, e.g., 21 C.F.R. § 320.24(a) (“bioequivalence may be demonstrated by several in vivo and in vitro methods”). Moreover, as explained above, no in vitro system has ever been validated to emulate either the tear fluid or the environmental conditions of the eye, and review of the scientific literature confirms that no scientifically valid methods are currently available for substituting in vitro for clinical testing in this area. FDA itself has recognized the need for special attention to drug products, like RESTASIS, that raise “novel” or “complex” bioequivalence issues. See FDA, Guidance for Industry, Bioequivalence Recommendations for Specific Products 2–3 (June 2010). Importantly, as discussed above, the Agency has in fact commissioned research—which is currently ongoing—to investigate potential new methods for assessing bioequivalence of ophthalmic emulsions, precisely because of the gap that currently exists in our scientific understanding in that area. If that research is successful, perhaps in the future FDA will be able, through rulemaking, to establish new scientifically valid methods to show bioequivalence in ophthalmic emulsions. At present, however, FDA plainly has not done so.

Relatedly, while the Draft Guidance recommends the use of comparative-release testing, it suggests no method by which this might be accomplished. No such method—and certainly no establish, scientifically valid method—is known to exist. There is no evidence for the
proposition that the physicochemical and drug-release studies suggested in the Draft Guidance could accurately reflect the rate and extent to which cyclosporine from an ophthalmic emulsion becomes available at the site of drug action. Nor is there any evidence that products so formulated would necessarily be bioequivalent to, or be as safe or effective as, RESTASIS. To the contrary, statements from FDA and others confirm that this is not the case. Indeed, the complex ophthalmic environment itself suggests as much, as there is presently no release-testing method that can differentiate performance in the timescale required, where the active drug is available for transcorneal penetration in the span of a few blinks, and eye-drops are quickly eliminated through nasolacrimal drainage.

B. FDA Is Bound By Its Own Regulations To Require Clinical Testing Here

It is “axiomatic that an agency is bound by its own regulations.” Panhandle Eastern Pipe Line Co. v. FERC, 613 F.2d 1120, 1135 (D.C. Cir. 1979). Although an agency has broad discretion to interpret its regulations, Talk America, Inc. v. Michigan Bell Telephone Co., 131 S. Ct. 2254, 2261 (2011), it may not deviate from its regulations or change a definitive regulatory interpretation through non-binding guidance without providing notice and an opportunity for comment. See Mortgage Bankers Ass’n v. Harris, No. 12–5246, 2013 WL 3305719, *1 (D.C. Cir. Jul. 2, 2013).

As discussed above, the Draft Guidance ignores and fails to comply with applicable statutory requirements. In addition to violating the FDCA, approving an ANDA referring to RESTASIS without requiring in vivo testing would violate the regulations. FDA is required under 21 C.F.R. § 320.33 to consider “[c]riteria and evidence to assess actual or potential bioequivalence problems” when determining whether in vivo testing is necessary to establish bioequivalence. Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 217 (D.D.C. 1996) (noting 21 C.F.R. § 320.33). This includes “[e]vidence from well-controlled bioequivalence studies that such products are not bioequivalent drug products,” and a “[c]ompetent medical determination that a lack of bioequivalence would have a serious adverse effect in the treatment or prevention of a serious disease or condition.” 21 C.F.R. § 320.33(b) and (d). FDA likewise must consider physicochemical evidence of several factors, including that “[t]he active drug ingredient has a low solubility in water,” id. § 320.33(e)(1); “[t]he particle size . . . of the active drug ingredient is critical in determining its bioavailability,” id. § 320.33(e)(3); “physical structural characteristics of the active drug ingredient . . . dissolve poorly and this poor dissolution may affect absorption,” id. § 320.33(e)(4); and “[s]pecific inactive ingredients . . . if present, may interfere with such absorption.” Id. § 320.33(e)(6).

All of these recognized “problem” factors are present here. Allergan’s experimental studies provide clear evidence that cyclosporine ophthalmic emulsions may satisfy the Draft Guidance but in fact not be bioequivalent to RESTASIS. It is equally clear that dry eye disease is a serious disease and, if untreated or treated with inadequate medication, the disease could lead to significant adverse consequences for patients. Further, as discussed in detail above, because a substantial fraction of cyclosporine is absorbed by the tissues from clear phases of the emulsion, globule size distribution size is particularly relevant to bioavailability here. Globule
size distribution, although significant, is only one factor that ensures that the drug reaches, enters, and functions at the necessary site or sites of action. The Draft Guidance suggests that FDA believes that only total drug-quantity from an emulsion formulation needs to be considered, but that is incorrect. The quantity of the drug in different types of globules in different phases of the emulsion must be considered as well.

In any event, as a general matter, in vivo studies are required to establish bioequivalence even under FDA’s regulations. See 21 C.F.R. § 320.22(a) (referring to “the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the drug product”); see also 57 Fed. Reg. at 17,976 (“[i]n general, the submission of in vivo data is required”). FDA has promulgated a regulation that states that at the request of an ANDA applicant, FDA may “waive the requirement for the submission of evidence . . . demonstrating the in vivo bioequivalence of the drug product that is the subject of the application.” 21 C.F.R. § 320.22(a). But another regulation makes clear that such a waiver must be supported by “good cause” and must be “compatible with the protection of the public health.” Id. § 320.22(e).

The in vivo testing requirement cannot be waived here because any waiver would be incompatible with “the protection of the public health.” Dry eye disease is a serious and progressive disease. If untreated or treated with ineffective medication, dry eye disease can lead to severe eye damage (including inflammation, corneal infection, and scarring) and vision loss. At the same time, patients who use cyclosporine may be elderly and, in addition to dry eye, may have multiple ocular complications. RESTASIS is indicated to slow or halt the disease. Over the last ten years, there have been approximately 8.5 million patient-years of exposure worldwide, and there have been no significant treatment-related systemic adverse events associated with RESTASIS when used by patients for up to three years.

While RESTASIS is undeniably safe and effective, the same cannot be said of cyclosporine ophthalmic emulsions formulated using the Draft Guidance parameters. Allergan’s alternative-formulation testing shows that emulsions falling within those parameters have different quantities of cyclosporine in different phases; live animal studies confirm that such emulsions are tolerated differently. Moreover, for dry eye disease, the specific target tissues are not clear, and the exact concentration of cyclosporine that needs to be delivered to each of those tissues is likewise unknown. Consequently, there is no scientific basis to assume that the parameters offered in the Draft Guidance would accurately assess drug safety or effectiveness, and there is empirical evidence to the contrary.

For these same reasons, if FDA approved a generic version of RESTASIS based on the Draft Guidance, the agency would abuse its discretion under 21 C.F.R. § 320.24(c). Paragraph (c)(1) of the regulation provides that the agency may “require in vivo testing in humans of a product at any time if the agency has evidence that the product” “[m]ay not produce therapeutic effects comparable to a pharmaceutical equivalent or alternative with which it is intended to be used interchangeably.” Paragraph (c)(3) provides that the agency may require in vivo testing when
there is “greater than anticipated potential toxicity related to pharmacokinetic or other characteristics.” 21 C.F.R. § 320.24(c)(1) and (3). In light of the foregoing evidence, FDA’s own regulations make in vivo testing appropriate. See 5 U.S.C. § 706(2)(A) (a reviewing court “shall hold unlawful and set aside agency action . . . found to be . . . an abuse of discretion”).

C. FDA Has Long Required In Vivo Testing For Topical Emulsions And It Cannot Change Its Position Without A Reasoned Explanation

In light of FDA’s long-standing recognition that in vivo data is needed to establish bioequivalence for locally acting topical products including ophthalmic drugs, see Section III.A., the agency cannot rely solely on in vitro data to establish bioequivalence without providing a carefully reasoned explanation. Under the current state of the science, it is unexplained and inexplicable why the agency has changed its position for purposes of determining bioequivalence to RESTASIS. Allowing bioequivalence to be shown solely through in vitro data is a complete departure not only from FDA’s past statements of policy, but also from known scientific principles demonstrating that, at this time, in vitro data are not sufficient to assess bioequivalence in these types of products.

In any event, regardless of FDA’s reasons for deviating from its prior stated position, it cannot execute a change in policy in the manner it has done here. FDA cannot just “depart from prior policy sub silentio or simply disregard rules that are still on the books.” FCC v. Fox Television Stations, Inc., 556 U.S. 502, 515 (2009). Any change in position requires “a reasoned explanation . . . for disregarding facts and circumstances that underlay or were engendered by prior policy,” especially in circumstances where an agency’s “new policy rests upon factual findings that contradict those which underlay its prior policy; or when its prior policy has engendered serious reliance interests that must be taken into account.” Id. at 515-16. FDA has provided no such explanation. Instead, it has issued a draft guidance that discards its past position with little, if any, explanation or scientific support. To change a long-standing policy in this way is an arbitrary and capricious exercise of agency power that is contrary to the law. See Nat’l Ass’n of Regulatory Utility Comm’rs v. U.S. Dept. of Energy, 680 F.3d 819, 825 (D.C. Cir. 2012) (“an unexplained departure from long-standing [agency] policy” is arbitrary and capricious).

D. Any Approval Made In Accordance With The Draft Guidance Would Be Arbitrary And Capricious

An agency’s decision must be set aside if it is “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.” 5 U.S.C. § 706(2)(A). The agency violates those requirements if it fails to articulate a “rational connection between the facts found and the choice made,” Florida Gas Transmission Co. v. FERC, 604 F.3d 636, 639 (D.C. Cir. 2010); departs from precedent without reasoned explanation, FCC v. Fox Television Stations, Inc., 556 U.S. 502, 516 (2009); or fails “to consider an important aspect of the problem,” Motor Vehicle Mfrs. Ass’n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983). Moreover, an agency must provide a
reasoned explanation for its regulatory actions. See, e.g., id. at 48, 52 (observing that “an agency must cogently explain why it has exercised its discretion in a given manner,” and that the explanation must be “sufficient to enable [the Court] to conclude that the [agency’s action] was the product of reasoned decisionmaking”); A.L. Pharma, Inc. v. Shalala, 62 F.3d 1484, 1490 (D.C. Cir. 1995) (directing FDA to provide an adequate explanation of its determination that a particular study established bioequivalence). If FDA approves an ANDA without requiring clinical testing, that action would not be in accordance with law and would be arbitrary and capricious.

This Comment sets forth evidence in the core areas for assessing bioequivalence, namely, the complex physicochemical nature of the emulsion dosage form for cyclosporine as it interacts with, and within, the complex ophthalmic surface environment. As discussed above, neither the target tissues involved (which could include the cornea, conjunctiva, eyelid/meibomian glands, accessory lacrimal glands, and the regional draining lymph nodes) nor the concentration of cyclosporine that needs to be delivered to each of these tissues is well understood. There is presently no method by which to predict the appropriate therapeutic concentrations in the appropriate target tissues, because there is no way to assess accurately the interaction between the emulsion, the target tissues, and the tear composition of a diseased eye. Failure by FDA to consider and justify its position in the Draft Guidance in light of such evidence would be arbitrary and capricious. See PSEG Energy Res. & Trade LLC v. FERC, 665 F.3d 203, 208 (D.C. Cir. 2011) (“[a]n agency’s failure to respond meaningfully to objections raised by a party renders its decision arbitrary and capricious”); see also Guidance for Industry, Bioequivalence Recommendations for Specific Products 3 (June 2010) (“In assessing whether an ANDA contains adequate evidence of [bioequivalence], the Agency considers available relevant information, which may include information submitted by the public to dockets for citizen petitions and product-specific [bioequivalence] recommendations.”).

There is, moreover, no rational connection between in vitro and in vivo testing in this area, and there are no scientifically valid methods currently available that would allow the former to be substituted for the latter. To the contrary, there is no way to extrapolate bioequivalence, let alone comparable safety and effectiveness, from the physicochemical and drug-release studies suggested in the Draft Guidance. Such studies will not accurately reflect the rate and extent to which cyclosporine from an ophthalmic emulsion becomes available at the site of drug action. See, e.g., Florida Gas, 604 F.3d at 639 (holding that agency action is arbitrary, capricious, and not in accordance with law unless the agency articulates a “rational connection between the facts found and the choice made”).

The Draft Guidance misses the critical point that different phases of different emulsion formulations will contain varying sized globules (including micelles) that potentially deliver cyclosporine at different rates to the active sites. Thus, contrary to the approach in the Draft Guidance, ensuring comparable in vivo uptake and availability requires an accurate assessment of the size and quantity of globules in different emulsion phases, which the Draft Guidance’s approach would fail to achieve. See supra at 26; see, e.g., State Farm, 463 U.S. 29 at 52
(explaining that an agency’s action is arbitrary and capricious if the agency has “failed to consider an important aspect of the problem”).

While FDA is free to seek different approaches consistent with sound science and to commission research to help fill gaps in current scientific understanding, it is not free to adopt a new approach that does not satisfy the applicable statutory provisions, is not scientifically valid, and constitutes an unacknowledged and unjustified departure from the agency’s past position.

VIII. Conclusion

For the reasons set forth in this Comment, FDA should replace the Draft Guidance with revised guidance that makes clear that a proposed generic referring to RESTASIS must demonstrate bioequivalence through comparative clinical trials to show equivalent safety and effectiveness based on clinical endpoints.

Allergan is available to discuss our concerns or specific data with the agency.

Sincerely,

Richard Spivey
Sr. VP Global Regulatory Affairs
Allergan, Inc.

CC:
FDA, Office of Generic Drugs
Kathleen Uhl, M.D., Acting Director
Robert Lionberger, Ph.D., Acting Deputy Director for Science
Dale Conner, Pharm.D., Director, Division of Bioequivalence I
John Peters, M.D., Director, Division of Clinical Review

FDA, Office of New Drugs
Renata Albrecht, M.D., Director, Division of Transplant and Ophthalmology Products
Wiley Chambers, M.D., Deputy Director, Division of Transplant and Ophthalmology Products

FDA, Office of the Chief Counsel
Elizabeth Dickinson, Esq., Chief Counsel