

Impact of FDA Regulatory Research on the Landscape of Ophthalmology Drugs

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Ophthalmic Products
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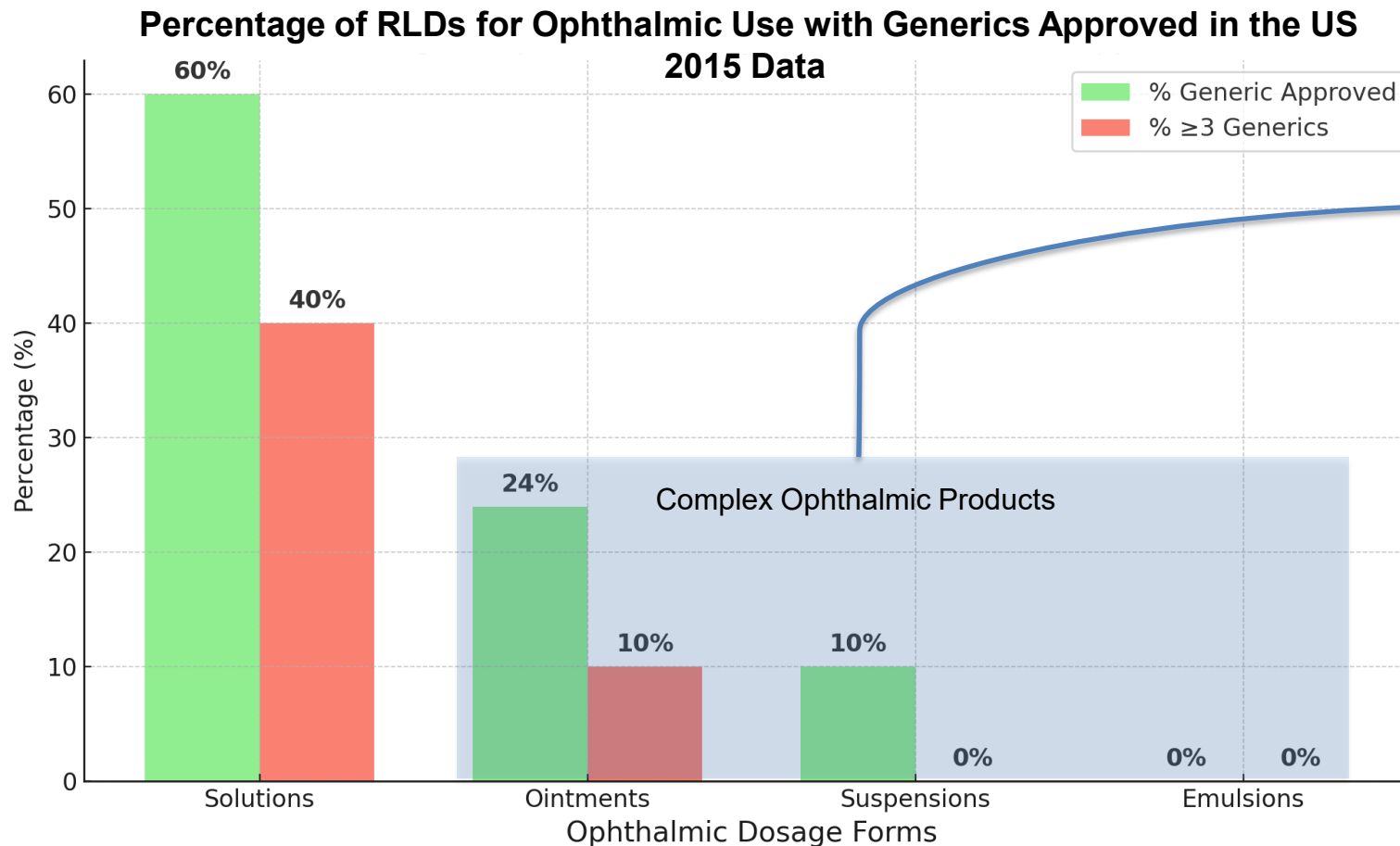
Presentation Overview

A brief look at FDA's past 10-year efforts to enhance and innovate bioequivalence standards for ophthalmic drug products

- Eye as a complex route of administration
- FDA's approach to understanding ophthalmic products via research
- Navigating Product Specific Guidances for ophthalmic products
- Reflecting on the past, evaluating the present, and envisioning the future of generic ophthalmic drug product standards

10 Years Ago...

A brief look at the ophthalmic generic drug product landscape in 2015

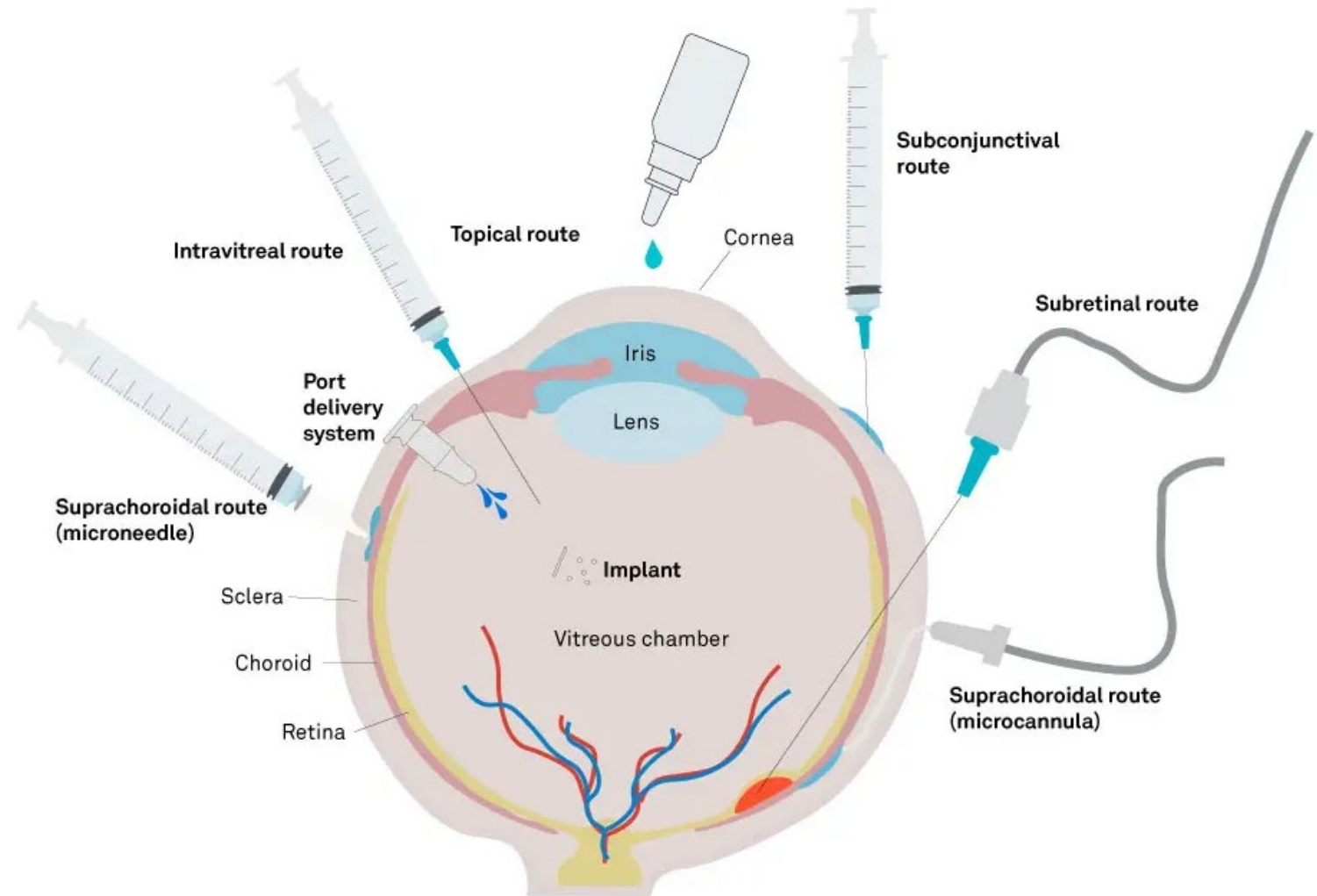


Call to Action!

Unmet need for pathways to enable approval of bioequivalent complex generic ophthalmic products, ensuring availability of safe, effective, and affordable medicines.

Eye: A Complex Route of Administration

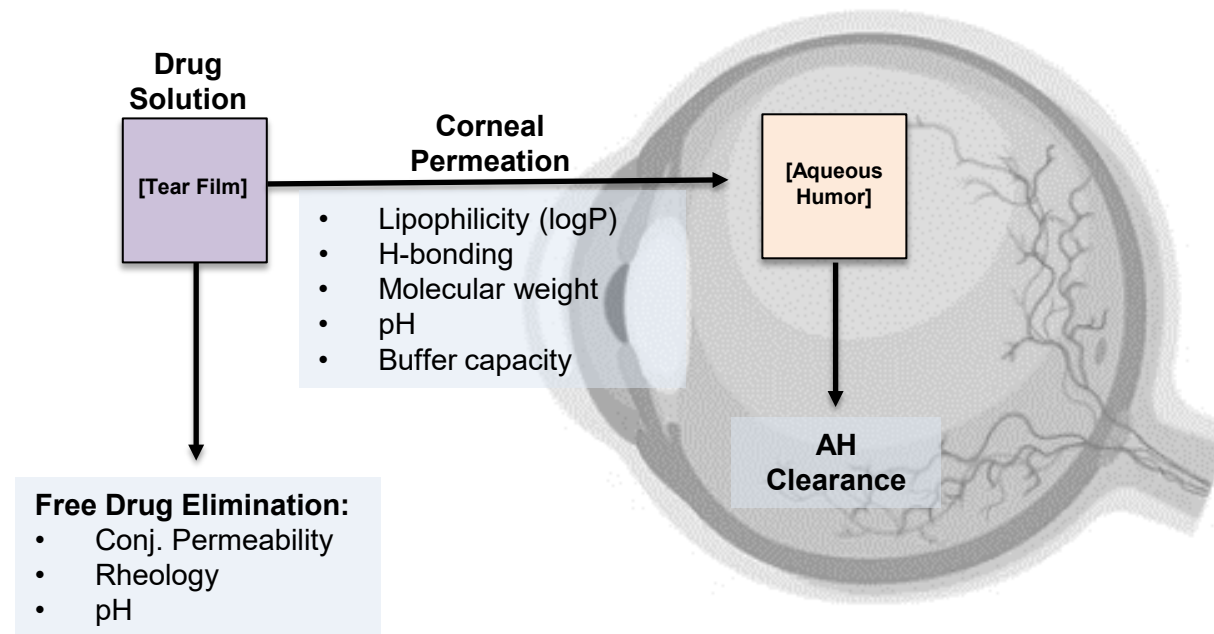
Bioavailability/bioequivalence of ocular formulations depends on a **complex interplay** among **formulation composition**, **physicochemical characteristics**, and **biological interface**



Ocular Product Performance (1)

FDA's understanding of how a product property can affect bioavailability of ophthalmic products has developed over a decade of research, and it is key to the development of alternate bioequivalence approaches that rely on the specific characteristics of the drug product, its intended use, and its interactions with the ocular environment.

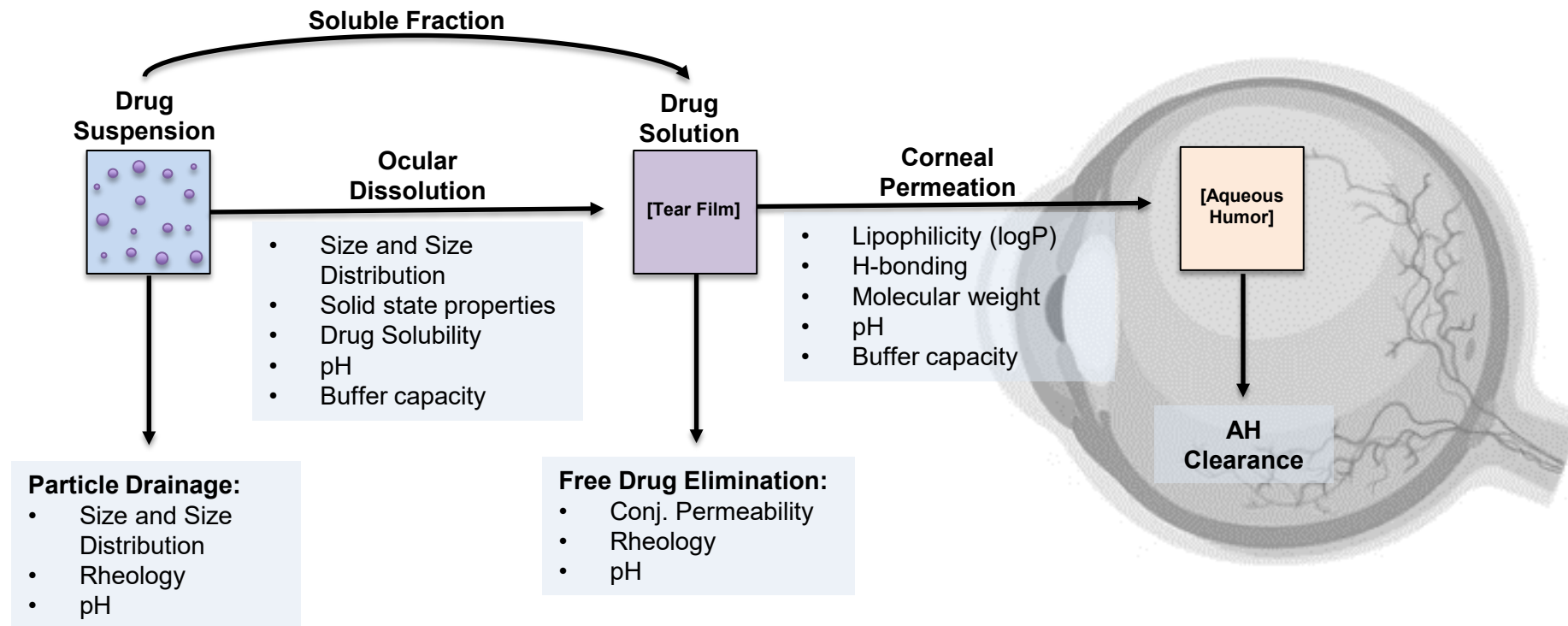
As a starting point, let's consider a typical topical ophthalmic solution intended to deliver the drug to the aqueous humor:



Ocular Product Performance (2)

As dosage forms increase in complexity, so does the level of information that needs to be understood and matched to ensure equivalency in drug product performance in the eye

As example, for a typical complex ophthalmic suspension intended to deliver the drug to the aqueous humor:



Product-specific thinking supports the development of Product Specific Guidances (PSGs) for at least 75% of complex ophthalmic NDA products within 3 years of approval by FDA.

Product Specific Guidances (PSGs) and GDUFA III



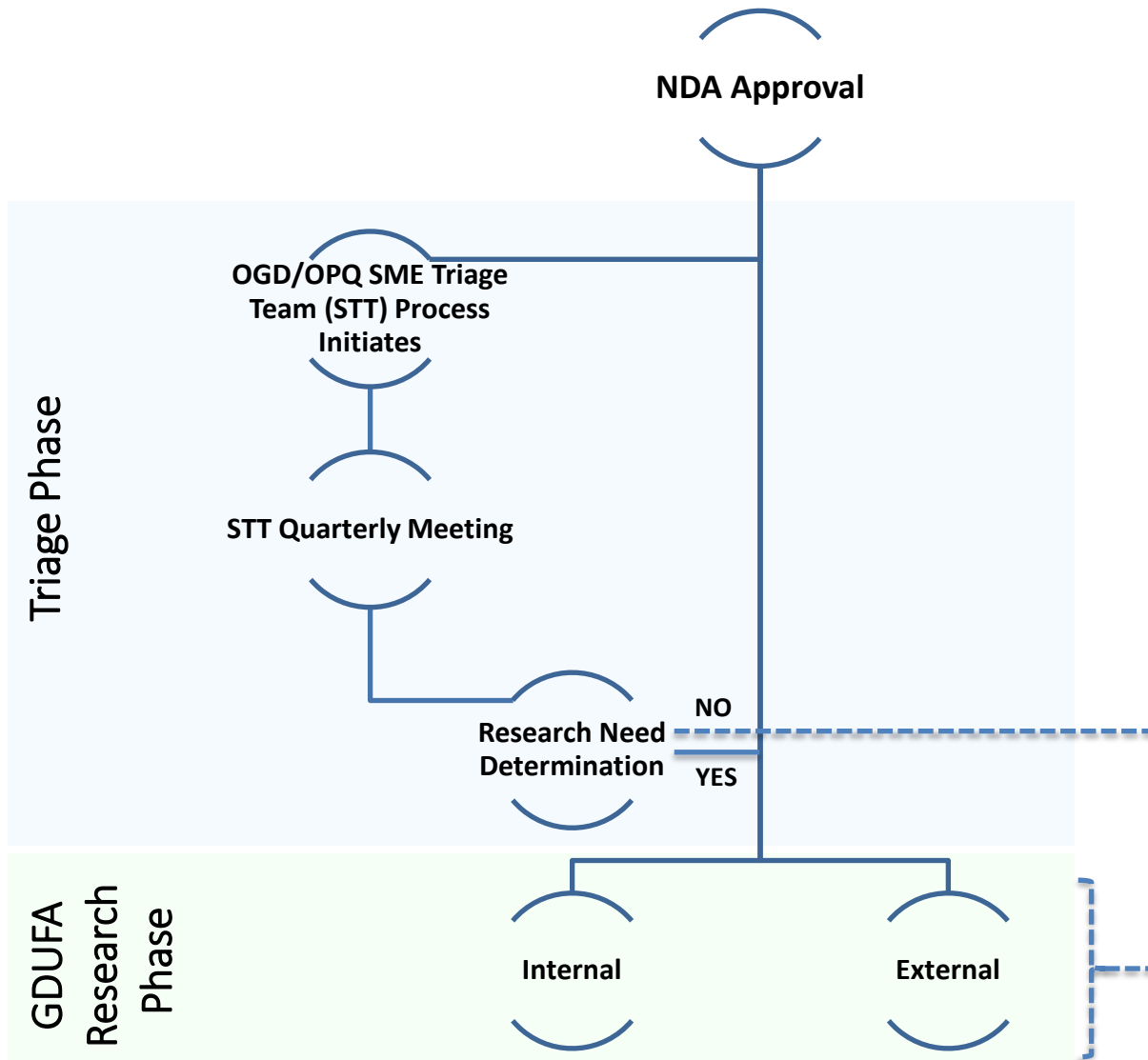
PSGs outline FDA's current product-specific thinking on the type of studies and information to support the development and approval of a therapeutic equivalent generic product to the RLD product.

Section III.C Product-Specific Guidance

1. FDA will continue to issue PSG identifying the methodology for generating evidence needed to support ANDA approval.
2. FDA will issue PSGs consistent with the following **goals**:
 - a. **For Complex Products approved in new drug applications (NDAs) on or after October 1, 2022, a PSG will be issued for 50 percent of such NDA products within 2 years after the date of approval, and for 75 percent of such NDA products within 3 years after the date of approval.**
 - b. FDA will continue to develop PSGs for Complex Products approved prior to October 1, 2022, for which no PSG has been published.
 - c. For non-complex drug products approved in NDAs on or after October 1, 2022, that contain a new chemical entity (NCE) (as described in section 505(j)(5)(F)(ii) of the FD&C Act), a PSG will be issued within 2 years after the date of approval for 90 percent of such products.

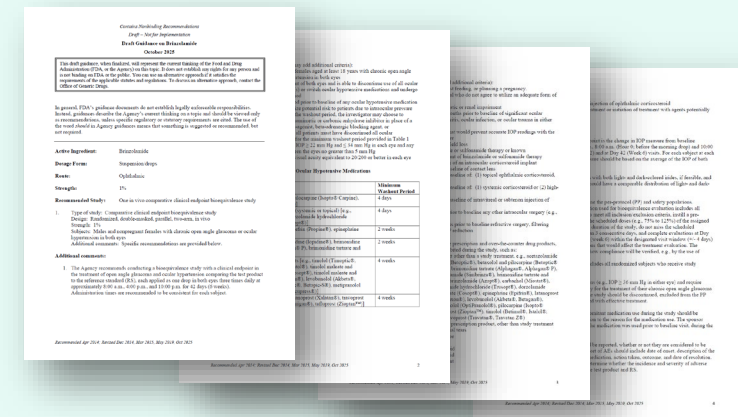
GDUFA III Commitment Letter: <https://www.fda.gov/media/153631/download>

PSG Development Process



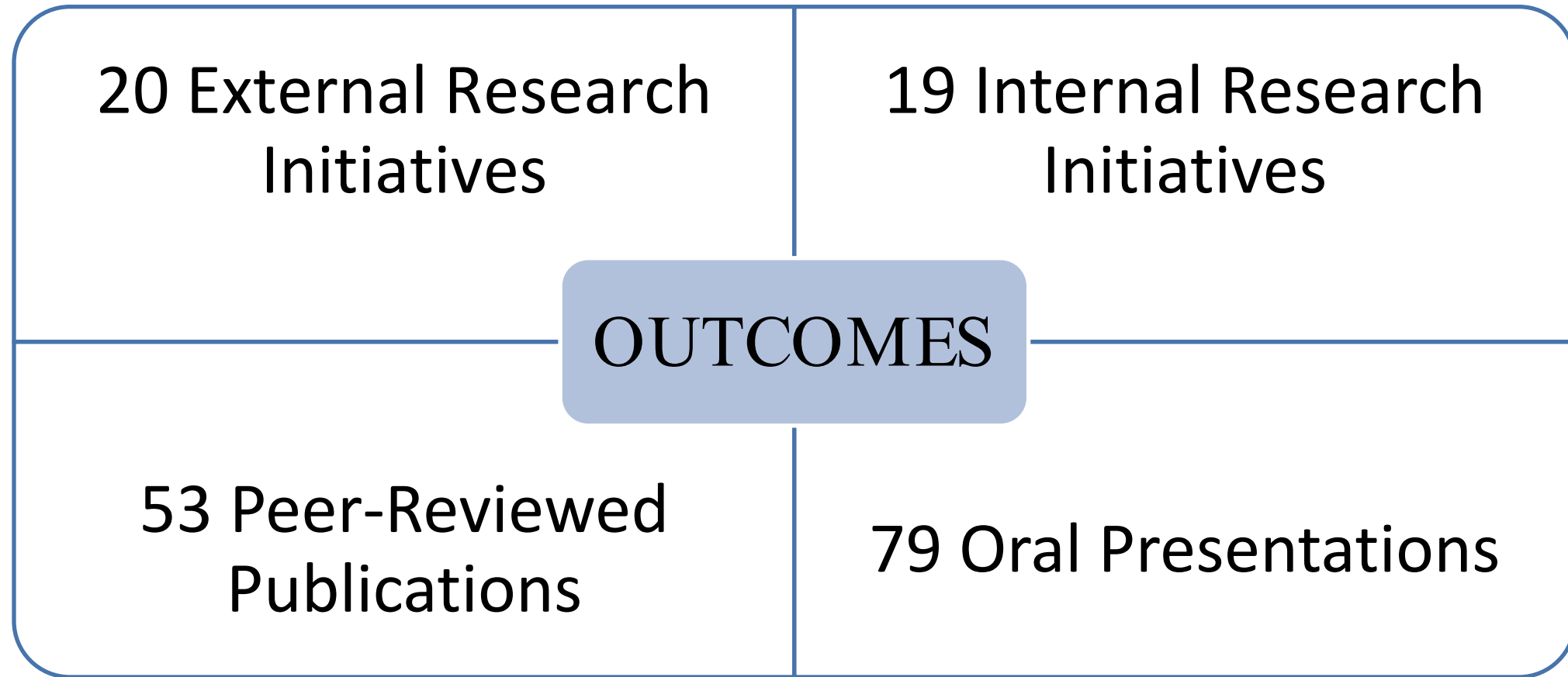
PSG Development and Publication Phase

- FDA integrates data from internal and external research.**
- FDA conducts cross-office scientific and legal reviews** ensure policy alignment and technical accuracy.
- Draft PSG is finalized** for internal clearance and publication preparation.
- Draft PSG announced in the Federal Register and posted on FDA's PSG website.**



Ophthalmic GDUFA Research in Numbers

(2015 → 2025)



Key Outcome: Ophthalmic PSGs

Ophthalmic PSGs recommending in vitro-based approaches, either alone or in combination with *in vivo* studies
(as of November 2025)

-Solution (70+) – request waiver of in vivo bioequivalence study requirements based on formulation qualitative and quantitative sameness and comparable formulation physicochemical characteristics

-Suspension (14)

- Besifloxacin Hydrochloride; 022308
- Dexamethasone; Neomycin; Polymyxin B; 050023
- Dexamethasone; Tobramycin; 050818
- Dexamethasone; Tobramycin; 050592
- Fluorometholone; 019216
- Fluorometholone; 016851
- Fluorometholone Acetate; 019079
- Loteprednol Etabonate; 210565
- Loteprednol Etabonate; 020803
- Loteprednol Etabonate; 020583
- Nepafenac; 021862
- Nepafenac; 203491
- Prednisolone Acetate; 017011
- Triamcinolone acetonide; 022048

-Emulsion (3)

- Cyclosporine; 050790, 214965
- Difluprednate; 022212

-Gel (6)

- Chlorprocaine hydrochloride; 216227
- Ganciclovir; 022211
- Loteprednol Etabonate; 202872, 208219
- Lidocaine hydrochloride; 022221
- Timolol maleate (gel forming sol); 020330

-Ointment (8)

- Acyclovir; 202408
- Bacitracin; 061212
- Ciprofloxacin Hydrochloride; 020369
- Dexamethasone; Tobramycin; 050616
- Dexamethasone; Neomycin Sulfate; Polymyxin B Sulfate; 050065
- Erythromycin; 062447
- Loteprednol Etabonate; 200738
- Tobramycin; 050555

-Implants/Inserts (2)

- Dexamethasone; 022315
- Travoprost; 218010

Navigating Ophthalmic PSGs (1)

Draft Guidance on Loteprednol Etabonate February 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Loteprednol etabonate
Dosage Form:	Suspension/drops
Route:	Ophthalmic
Strength:	0.5%
Recommended Studies:	Two options: (1) two in vitro bioequivalence studies with supportive comparative characterization studies, or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: Two in vitro bioequivalence studies with supportive comparative characterization studies

To demonstrate bioequivalence by this option, the test product should be qualitatively (Q1)¹ and quantitatively (Q2)² the same as the reference listed drug (RLD).³

Two selective options for demonstrating bioequivalence

Formulation eligibility considerations

(In vitro-only totality of evidence approaches recommended for Q1/Q2 formulations)

Navigating Ophthalmic PSGs (2)

Two in vitro bioequivalence studies:

1. Type of study: Drug particle size and particle size distribution of loteprednol etabonate
Design: In vitro bioequivalence study on three batches of both test and reference standard (RS) products
Strength: 0.5%

Additional comments: The sample preparation method and selected particle sizing methodology should be adequately optimized and validated to demonstrate the adequacy of the selected method in accurately and reliably identifying and measuring the size of the drug particles. Prospective applicant should perform size characterization at different dilution conditions as part of method development to demonstrate the impact of dilution. Full particle size distribution profiles representative of all test product and RS product batches tested should be submitted as supporting information.

Parameters to measure: D_{50} and SPAN $[(D_{90}-D_{10})/D_{50}]$

Bioequivalence based on (95% upper confidence bound): Population bioequivalence (PBE) analysis of the D_{50} and SPAN. Prospective applicants should provide no less than 10 datasets from three batches each of the test and RS products to be used in the PBE analysis. For additional information on PBE statistical analysis, refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929).^a

2. Type of study: Comparative in vitro release testing (IVRT) of loteprednol etabonate
Design: Should be performed on three batches of both test and RS products using at least 12 units from each batch
Strengths: 0.5%

Additional comments: The IVRT method study should include information on the method development and validation to detect potential formulation differences and capture the complete release profile of loteprednol etabonate.

Bioequivalence based on: Comparative analysis of release profiles should be established using an appropriate statistical method (e.g., model independent approach using similarity factor (f_2)). For more information on calculation of f_2 factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.^b

Two Pivotal In Vitro Bioequivalence Studies

- **Drug particle size and size distribution:**
 - A critical determinant of drug dissolution, generally the rate-limiting step for ocular bioavailability in ophthalmic suspensions.
 - A strict statistical comparison of particle size distribution between Test and RS products is recommended.
- **In Vitro Drug Release Testing:**
 - It should employ a discriminative methodology sensitive to factors affecting in vivo performance.
 - Key variables generally include drug particle size and formulation viscosity.

Navigating Ophthalmic PSGs (3)



Comparative characterization studies:

Comparative physicochemical characterization of the test and RS products. The comparative study should be performed on at least three batches of both the test⁴ and RS products and should include:

- a. Appearance
- b. pH
- c. Specific gravity
- d. Osmolality
- e. Surface tension
- f. Viscosity
- g. Soluble fraction of loteprednol etabonate in the finished drug product

II. Option 2: One in vivo bioequivalence study

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
Design: Single-dose, crossover or parallel design in vivo in aqueous humor
Strength: 0.5%
Subjects: Patients undergoing cataract surgery and scheduled to receive ophthalmic corticosteroids just prior to eye surgery

Analyte to measure: Loteprednol etabonate in aqueous humor

Bioequivalence based on (90% CI): Loteprednol etabonate

Supportive Comparative Characterization Studies:

- **pH and Osmolality:** Key indicators of ocular irritation potential; may influence tearing and patient comfort.
- **Surface Tension:** Assesses formulation stabilizer and its variations.
- **Viscosity and Rheology:** correlates with residence time on the ocular surface; rheological behavior should be evaluated across shear rates.
- **Soluble fraction:** reflects drug solubilization in finished product, influencing absorption rate and overall bioavailability

Alternatively, ***in vivo* bioequivalence study option** may also be recommended for Q1/Q2 and non-Q1/Q2 formulations

[as per 21 CFR 314.94(a)(9)(iv)]*

*FDA may consider scientifically-justified exceptions to its general recommendation that any Q1/Q2 difference in ophthalmic products necessitates an in vivo BE study(ies), as per FDA Guidance for Industry *ANDA Submissions -- Refuse-to-Receive Standards*. **Pre-ANDA process can be used to seek the Agency's concurrence to such cases prior to ANDA submission.**

Navigating Ophthalmic PSGs (4)



Additional information:

Device:

The RLD is presented in a bottle with a dropper tip. The bottle with dropper tip is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test device.

User interface assessment:

An abbreviated new drug application for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.^b

Quality assessment:

For quality-related recommendations for supporting drug product development, refer to the most recent version of the FDA guidance for industry on *Quality Considerations for Topical Ophthalmic Drug Products*.^b

Drug-Device Combination Products

Language identifying the device constituent part of the drug product, as well as recommendations for user interface assessment, are included in all PSGs for DDCPs for ophthalmic use.

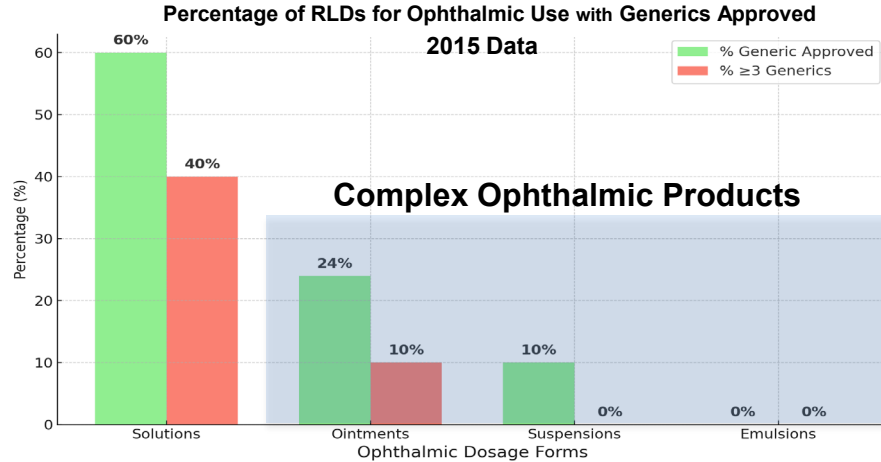
Quality Assessment

Among other quality considerations, recommendations pertaining to “drop size” and “dose homogeneity” are no longer outlined in PSGs. Instead, such parameters are recommended as part of quality-related recommendations and outlined in a centralized general guidance.

Impact on Ophthalmic ANDA Approvals

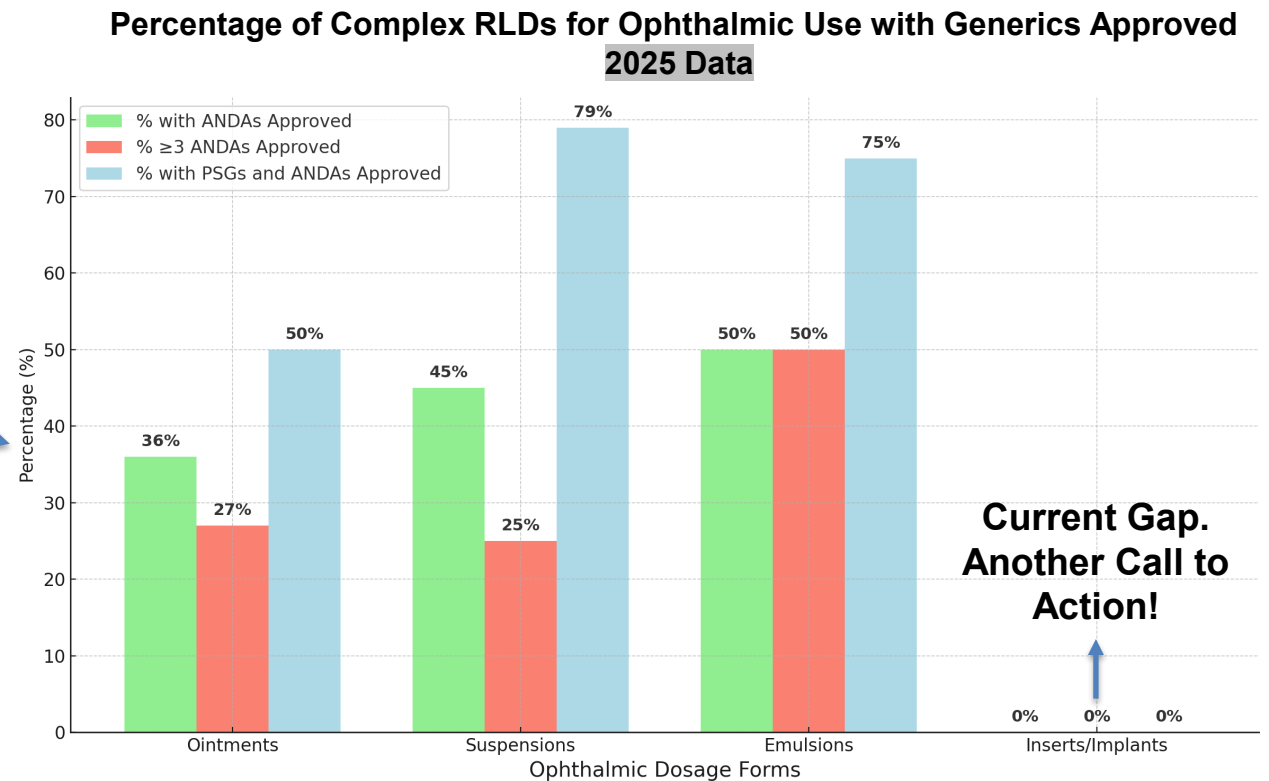


(2015 → 2025)



The publication of ophthalmic PSGs directly correlates with increased generic competition and improved access to ophthalmic drugs.

Industry actively leverages PSG recommendations, leading to greater availability of generics for RLDs with published PSGs.



Data collection from 1/1980 – 1/2025 – Complex Products Database and Orange Book

Envisioning the Future of Ophthalmic Generic Drugs



- Regulatory research and advanced analytical tools, including modeling, will continue to be developed and leveraged to assess the clinical impact of product properties and ingredients, driving the development of a more clinically relevant panel of in vitro tests and acceptance criteria. This will allow clinically-informed in vitro bioequivalence approaches to be established for ophthalmic products, facilitating generic drug development and approval without introducing clinical risks.
- Advancing regulatory science to support bioequivalence expectations for a novel class of complex ophthalmic dosage forms, implants and inserts, with the goal of facilitating development of product specific guidances that address the unique challenges of these technologies.
- Expansion of currently-established in vitro bioequivalence approaches to higher-risk ophthalmic drug product categories.
 - Be on the lookout for upcoming PSGs at <https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-generic-drug-product-development>

Acknowledgements



Deep appreciation is extended to all current and former FDA colleagues, fellows, and collaborators — both within and outside the Agency — who, over the past 10 years, have contributed meaningfully to advance generic ophthalmic drug product standards in service of the American people.