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The Altascientist

SCIENTIFIC JOURNAL

ISSUE NO. 43

# ADVANCING VISION CARE WITH FORMULATION AND MANUFACTURE OF OCULAR THERAPEUTICS

According to the WHO, at least a billion people are currently living with vision impairment from a preventable or treatable source. The main conditions causing their distance vision impairment or blindness are listed below.

**Common Eye Diseases (Global Prevalence)**

- **Cataract** . . . . . **(94 million)**
- **Refractive error** . . . . . **(88.4 million)**
- **Age-related macular degeneration** . . . **(8 million)**
- **Glaucoma** . . . . . **(7.7 million)**
- **Diabetic retinopathy** . . . . . **(3.9 million)**
- **Presbyopia** . . . . . **(826 million)**

Precedence Research reports that the global ophthalmic drug market size is estimated to double in 10 years, from $34.6 billion in 2021 to an estimated $68.93 billion by 2030. The development of pharmacological interventions for many of these conditions has been accelerating, supported by new delivery methods and formulation approaches. For conditions that require surgery or corrective devices, eye drops are an important part of diagnosis, and pre- and post-surgery treatment plans.

## IN THIS ISSUE

We explore how to meet the challenges of formulation development for ocular therapies.

# RECENT DEVELOPMENTS IN OPHTHALMIC MEDICATIONS

The ophthalmic market has experienced a recent surge of new drug approvals, treating conditions such as age-related macular degeneration (AMD), dry eye disease, geographic atrophy, retinopathy in premature birth, mydriasis, and others. These approvals provide new opportunities for drug development, and bring relief to patients suffering from eye disorders.

Some new drugs are reformulations of existing active pharmaceutical ingredients (APIs), formulated in a way that makes the drug easier to administer, and provide patent extension for the drug sponsor. Formulating existing drugs in combination with one another offers a similar opportunity for patent extension.

Engaging with an expert in ocular drug formulation and manufacturing who understands the intricacies and challenges of ophthalmic drug development and will deliver maximum efficiency to the process, is a valuable asset for drug sponsors.

# UNIQUE BARRIERS FOR DRUG DELIVERY TO THE EYE

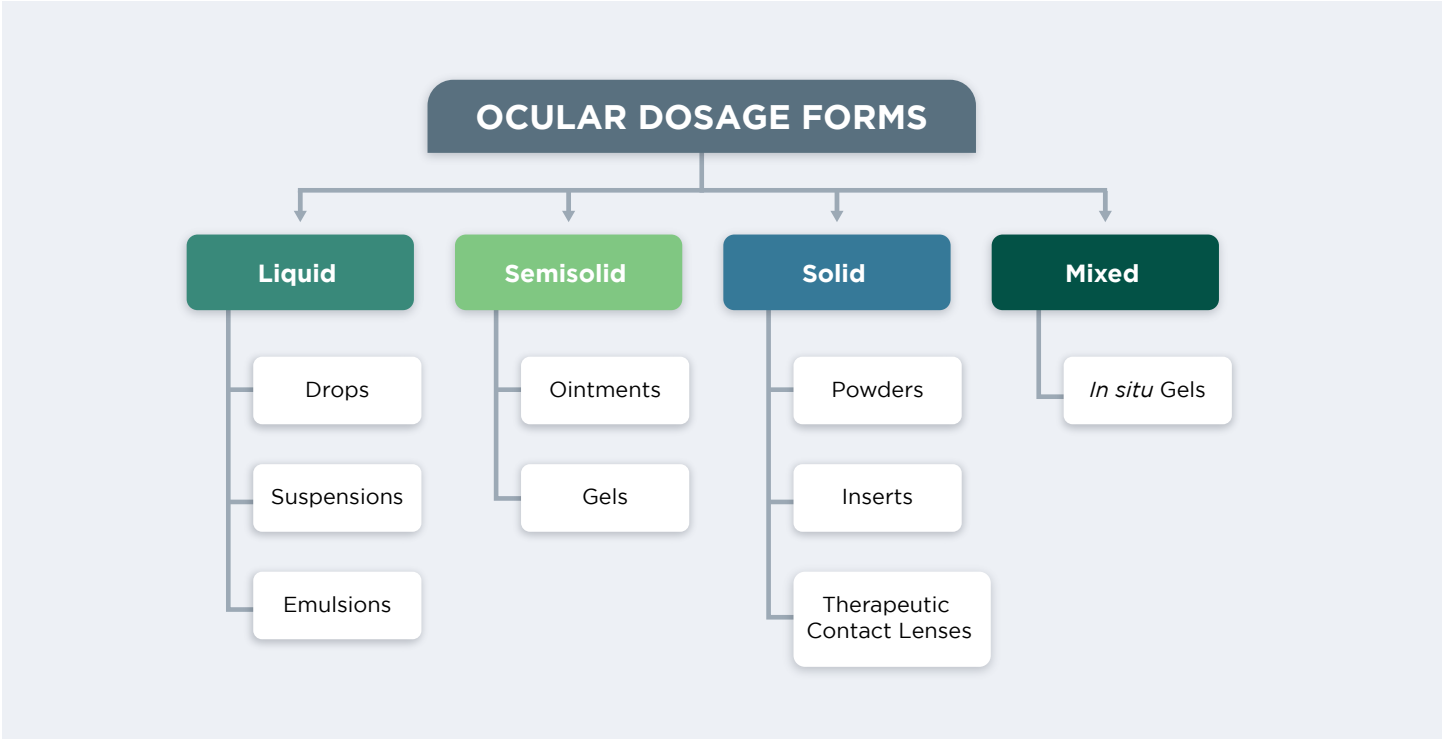
The eye has natural anatomical barriers that restrict the amount of medication reaching its intended target. These include the cornea's outer layer, the conjunctiva, and the blood-aqueous and blood-retinal barriers. These structures resist water-based drugs, limit absorption, and tightly regulate what enters the inner eye. Additionally, the eye's rapid tear film turnover continuously flushes out medication.

These barriers pose challenges for effective treatment—challenges that formulation specialists are striving to address with different formulation options.

# COMMON TYPES OF OCULAR FORMULATIONS

- **Eye drops:** A liquid formulation; the most common type of ocular drug. Eye drops are non-invasive and immediately active. Some eye drops combine two active ingredients, requiring specialized formulation expertise.
- **Suspensions:** A non-invasive topical drop that disperses finely divided insoluble drugs in an aqueous solvent.
- **Emulsions:** An emulsion-based formulation can improve the solubility and bioavailability of drugs. In an emulsion, one liquid is dispersed in the other using specific transforming processes.
- **Ointments:** A semi-solid formulation that is a mixture of a solid hydrocarbon and a semi-solid.
- **Gels:** A semi-solid formulation that can lengthen the residence time of the drug on the eye surface.
- **Solid dosage forms:** A formulation that can be used to deliver water-sensitive drugs, provide zero-order release, or sustain residence time.
  - These include **ocular films, inserts, and hydrogels**, where the drug is added as a solution or dispersion. Some examples include inserts (soluble or not), lenses coated with drug product (dissolving or not), oral dosages (rare), minitablets applied to the conjunctival sac, and collagen shields.

**Figure 1. Classification of Ocular Dosage Forms**




Available dosage forms have differing advantages and disadvantages, as shown in **Table 1**. Partnering with an expert CDMO that has experience with all the options ensures that formulation knowledge and experience provide the optimal approach for your drug.

**Table 1.**

| CARRIER | ADVANTAGES | LIMITATIONS |
|---|---|---|
| **Eye solutions** | • Easy to instill<br>• Convenient<br>• Economical | • Drainage from the eye<br>• Drug loss through tears<br>• Low bioavailability<br>• Requires repeated instillation |
| **Suspensions** | • Prolonged contact time<br>• Improved patient compliance<br>• Ideal for drugs with slow dissolution | • Drug properties decide performance<br>• Irritation due to particle size<br>• Loss of drug solutions and suspended articles |
| **Ointments** | • Prolonged contact time<br>• No tear dilution<br>• Improved stability<br>• Improved bioavailability<br>• Flexible drug choice | • Blurring of vision<br>• Sticking of eyelids<br>• Poor patient compliance |
| **Nanosuspensions** | • Stable<br>• Prolonged contact time<br>• Improved bioavailability<br>• Enhance solubility | • Excellent for poorly soluble drugs |
| **Ocular inserts** | • Comfortable<br>• Prolonged delivery<br>• Reduced dose frequency | • Difficult to insert and remove |
| **Liposomes** | • Stable<br>• Control drug release<br>• Reduced dosing frequency<br>• Improved bioavailability | • Stability problems<br>• Not reproducible<br>• Rapid clearance<br>• Uptake by conjunctival cells |
| **Niosomes** | • Stable<br>• Controlled drug release<br>• Reduced dosing frequency<br>• High entrapment efficiency | • Lower bioavailability in the case of uptake by conjunctival cells |
| **Nanoparticles** | • Small size<br>• Long shelf life<br>• Highly stable<br>• Improved bioavailability<br>• Reduced dosing frequency | • Particle contamination |
| **Microparticles** | • Stable<br>• Improved bioavailability<br>• Reduced dosing frequency | • Irritation<br>• Large particle size |
| **Implants** | • Biodegradable<br>• Non-toxic | • Surgical application |
| **Penetration enhancers** | • Promote penetration of drugs<br>• Improved bioavailability | • Toxicity and irritation<br>• Large concentration |
| **Hydrogels** | • Prolonged residence time<br>• Increase bioavailability | • Triggered by temperature, pH and Ionic strength |
| **Dendrimers** | • Small size<br>• Decreased dosing frequency<br>• Prolonged residence time<br>• Improved bioavailability | • Blurred vision |
| **Emulsions** | • Prolonged drug release | • Blurred vision<br>• Patient non-compliance |
| **Micro-emulsions** | • Stable<br>• Improved solubility<br>• Improved bioavailability<br>• Reduced dosing frequency | • Toxicity due to higher concentration |

# FORMULATION FOR EFFECTIVE OCULAR DRUG DELIVERY

Drug developers use several approaches to ocular drug development. One approach is improving the bioavailability of a topically applied medication. Another method is increasing the time the medication is in contact with the eye.

## Improving Bioavailability Through Nanotechnology

Improving the bioavailability of ocular medications is critical to address the barriers to drug absorption. Enhancing bioavailability ensures that a sufficient amount of medication reaches the target tissue within the eye to effectively treat an ocular condition.

**Nanosuspensions** are used to improve the bioavailability of insoluble or poorly soluble molecules. The API is first milled to reduce particle size, usually followed by dispersing in an aqueous solvent. Particle size is directly indicative of drug residence time and activity on the precorneal surface. Small particles replenish the drug absorbed by ocular tissue, while large particles are more easily retained and slow drug dissolution.

**Suspensions** require a drug to dissolve or release prior to absorption. Release, ocular residence time, and bioavailability of a drug all vary based on the physicochemical properties of the suspension. Nanosuspensions improve the bioavailability of hydrophobic drugs by increasing solubility and residence time. However, it must be noted that physical stability can be a challenge, and there is a potential for drug sedimentation.

**Expert analytical testing** of a sample of the in-process material confirms purity, particle size, and several other product quality criteria using leading-edge particle size analysis technology. With these tests, CDMOs can precisely quantify the API and ensure the material has been milled to the correct specifications for the intended use.

## Prolonging Retention Time

There are a few approaches to improve the retention of a topical drug in the eye.

- **Viscosity enhancers** increase the adherence of the drug to the eye, stabilizing it and slowing its elimination from the eye.
- **Mucoadhesives** enhance the time the drug stays on the cornea, allowing the drug product to act.
- **Gels and ointments** significantly enhance residence time versus liquid formulations, so they do not wash out with the same ease and speed.
- **Solid dosage forms** can deliver water-sensitive drugs, provide zero-order release, or sustain residence time.

# SYSTEMIC EXPOSURE OF TOPICAL OPHTHALMIC PREPARATIONS

Ophthalmic topical medications are highly concentrated and can be absorbed systemically due to the passage of medication through the nasolacrimal duct into the highly vascular nasal mucosa. Systemic exposure to eye drops occurs when the active ingredients in the drops are absorbed into the bloodstream. This can happen through the tear duct, the conjunctiva, or the skin around the eyes. Systemic exposure can produce side effects, which formulation scientists work to minimize.

## Factors that affect systemic exposure:

- **Eye drop characteristics**—The concentration of active ingredients in eye drops is usually high.
- **Administration technique**—The way eye drops are applied can affect how much product is absorbed.
- **Patient population**—Infants, pregnant and nursing women, and the elderly are more likely to experience systemic side effects.

## How to mitigate systemic side effects through formulation optimization:

- **Reduce drug concentration**—Use the lowest effective dose to minimize excess drug availability for systemic absorption.
- **Add viscosity agents**—Increase precorneal retention time, reducing drainage into the nasal cavity.
- **Use micro/nano delivery systems**—Encapsulate drugs in polymeric particles or emulsions to target ocular tissues and limit leakage.
- **Increase mucoadhesion**—Introduce polymers such as chitosan or Carbopol® to bind to the mucin layer, keeping the drug on the ocular surface longer.
- **Reduce drop volume** to 20-30uL to match the eye's tear film capacity.

# OCULAR GENE THERAPY

Ophthalmic gene therapy is a fairly recent development. It is used to treat inherited eye diseases that affect the retina or choroid. These diseases include Leber congenital amaurosis, retinitis pigmentosa, and Stargardt disease.

The eye is an ideal target for gene therapy as it is an immuno-privileged organ, and the eye's tight anatomical barriers make systemic contamination or off-target effects unlikely. The gene therapy is delivered directly into the eye using an injection, which can be performed subretinally or intravitreally.

# MANUFACTURING OCULAR DRUGS FOR CLINICAL TRIALS AND COMMERCIALIZATION

## Manufacturing Ocular Drugs for Clinical trials

Ocular medications manufactured for clinical trials consider all the points previously mentioned, maximizing the formulation for optimal delivery and efficacy while minimizing the related limitations. Additionally:

- They are produced in small batches.
- They are sterilized via the simplest and least costly method, aligned with the specifics of the molecule. Terminal sterilization by the methods shown in Figure 2 and Table 2 below, in which the product and all its packaging are treated together at the end of the manufacturing process, is the most cost-effective and simple approach.
  - Not all products can tolerate a terminal sterilization approach, and those drugs would require an aseptic manufacturing process, where all the elements of the production process are sterilized beforehand, and then assembled under aseptic conditions.
- Masking packaging for blinded studies is routine.

**Figure 2. Different Sterilization Methods for Ophthalmic Nanopharmaceutics**

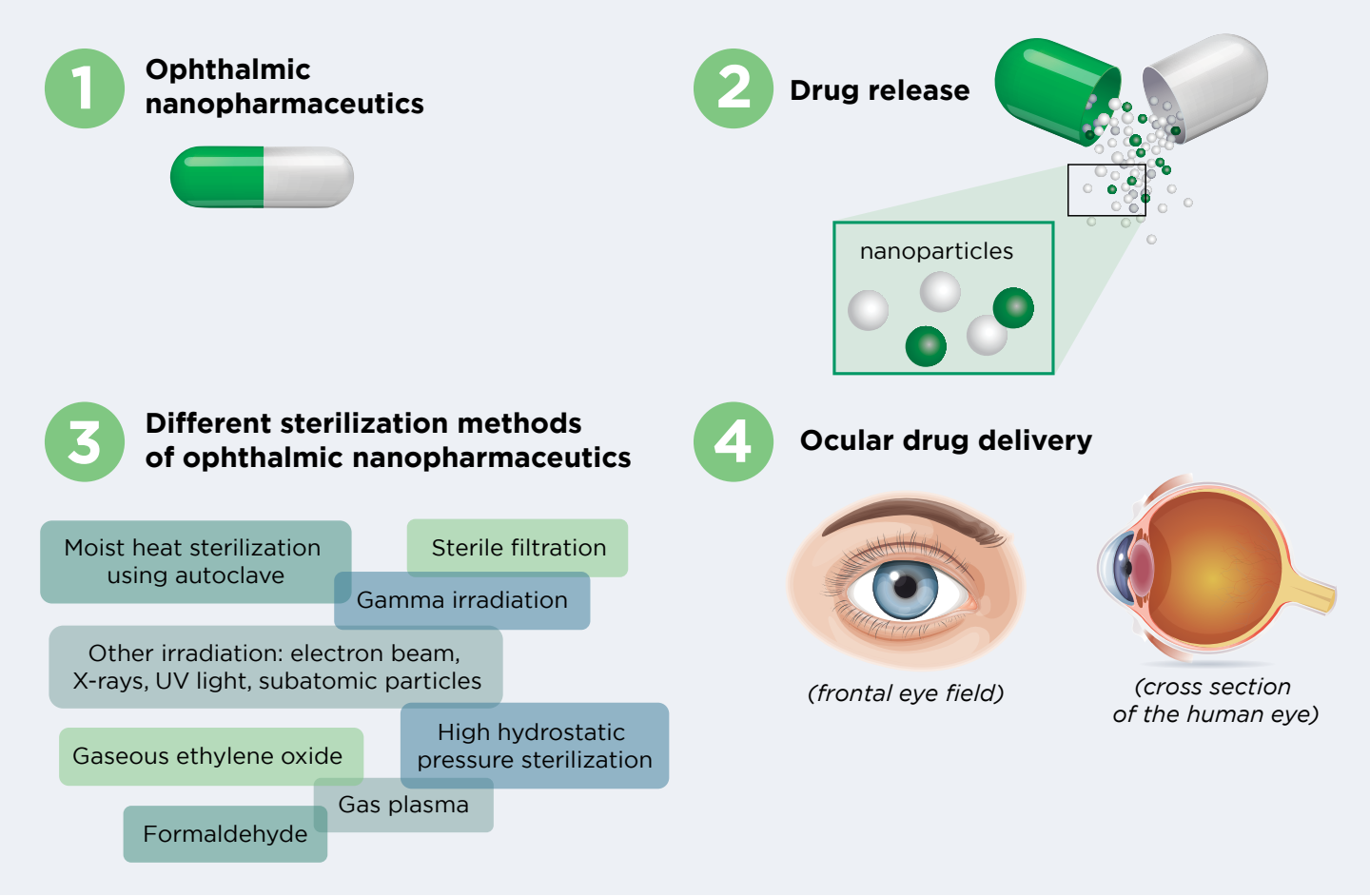


**Table 2. Advantages and Drawbacks of Different Sterilization Methods for Ophthalmic Drugs.**

| METHOD | EFFECT | ADVANTAGES | DRAWBACKS |
|---|---|---|---|
| Autoclaving, high-pressure steam | Bactericidal | Low cost | Chemical degradation, structural modification |
| Barrier filtration | Physical retention | Good for thermally sensitive drugs | Viscosity, size |
| Ionizing gamma irradiation | Damage of genetic material | Good for viscous material and thermally sensitive drug and adjuvant. No residue, effective against bacteria, yeast, fungus | Chemical degradation, free radical, rate of drug delivery, gas formation and high cost |
| Gaseous ethylene oxide | Bactericidal | Low cost, good for thermally sensitive drug and adjuvant | Toxic residue, cascade of oxidation, chemical change |
| High hydrostatic pressure | Affects the cellular structures and functions | Low cost | Toxicity through truncated proteins and carcinogens, affects redispersion |
| Gas plasma oxide reduction | Antimicrobial | Low temperature, nontoxic | Oxidative, causes aggregation |

## Manufacturing Ocular Drugs for Commercialization

Manufacturing topical eye medications for the commercial market involves critical considerations, most of which will have been tested and an approach determined during clinical testing. These factors include:

- **Sterility and contamination control**—Appropriate processing, sterilization, and preservative selection (if necessary) are essential, to meet regulatory requirements and ensure ultimate patient safety.
- **Long-term stability**—The formulation must maintain its stability over time, ensuring that active ingredients do not degrade and that any preservatives used remain effective.
- **pH and osmolarity adjustment**—Eye drops should be close to the eye's natural pH (~7.4) and osmolarity to reduce discomfort and avoid damaging ocular tissues.
- **Viscosity control**—Adjusting viscosity can enhance drug retention on the eye surface, improving efficacy while ensuring the solution is not too thick to cause discomfort or blurry vision.
- **Preservative vs. preservative-free options**—While preservatives help maintain sterility after opening, they can cause irritation for some users. Single-dose, preservative-free options are increasingly popular. For sponsors, the addition of a preservative-free option can create an opportunity for patent extension on the molecule.
- **Container and delivery system**—Packaging must protect the medication from contamination and degradation (e.g., UV-sensitive drugs), and allow for easy, controlled dispensing. Upgrades to the container or delivery system that could improve patient adherence may also provide an opportunity for patent extension for drug developers.
- **Manufacturing scalability and cost efficiency**—Large-scale production must balance cost, consistency, and quality control to ensure an affordable yet high-quality product that meets all regulatory requirements.

# ALTASCIENCES' CASE STUDY

## Comprehensive Customer Solutions

Altasciences has been **the trusted partner of a leading ocular pharmaceutical client for many years**, providing reliable manufacturing and testing of their ophthalmic drug products.

One of their ocular drugs required the use of **advanced technology and specialized manufacturing processes to meet strict particle size specifications**. Altasciences applied an integrated approach, combining expertise in logistics, manufacturing and analytical testing to meet the requirements.

Our significant contributions included:

1. **Efficient Procurement and Logistics Management:** Managed the procurement logistics for a range of excipients from various suppliers to ensure timely deliveries.
2. **Manufacturing of Product:** In our state-of-the-art Grade C compounding room, highly trained operators mixed the bulk product with precision, adhering to the client's exact formulation. With the flexibility to manufacture batch sizes ranging from 1 kilogram to 100 kilograms for ocular products (up to 2,000 kilograms for other therapeutic areas), we can scale to meet the demands of any project.

   For this particular client, a 7.4-kilogram batch was processed, incorporating advanced equipment like the NETZSCH-engineered DeltaVita® mills, which allowed us to reduce the API particles to meet nano-sized specifications.
3. **Rigorous Analytical Testing:** A representative sample from the production batch was subjected to extensive in-process testing in our on-site analytical lab. Using cutting-edge spectrophotometric, chromatographic, and particle size analyzer technologies, we meticulously tested for purity, particle size, and several other quality metrics.
4. **Terminal Sterilization:** After the product was tested and verified, we prepared the bulk material for terminal sterilization. This step is a crucial requirement for patient safety and regulatory compliance.

By leveraging our capabilities in drug manufacturing and analytical testing, we delivered a high-quality product that met all of the client's stringent requirements and the rigorous standards of the ophthalmic pharmaceutical industry.

# HOW ALTASCIENCES CAN HELP

With a deep understanding of regulatory requirements for ophthalmic formulations and cutting-edge manufacturing techniques, we provide comprehensive services tailored to meet the highest industry standards. Our team of experts is dedicated to ensuring product safety and consistency at every stage of development and production. We offer customized solutions that align with your specific needs, providing an optimized suite of services to deliver high-quality ophthalmic drugs for clinical trials or commercial use. Flip to the next page to discover our range of specialized ocular drug manufacturing services designed to support your success.

## Seamless transition from proof-of-concept formulations to clinical manufacturing

- Potent compounds and controlled substances
- Class C Manufacturing suites for development and clinical/commercial batches
- Flexible filling options, including vials, droppers, and custom containers
- Scale options from small batches up to 400L
- Milling capabilities for micro- and nanosuspension products
- Expert analytical support for method development, validation, and ICH stability testing

## All ophthalmic products, including potent compounds and controlled substances

- Liquids, gels, injectables, or capsules
- Formulation development to commercialization
- Analytical method development through validation and ICH stability testing

**Topical administration**

**Intraocular implants**

- **Systemic administration**
- **Subretinal injections**
- **Intravitreal injections**
- **Suprachoroidal injections**

## Experience working with complex drug products

- Emulsions
- Suspensions
- Complex powder blends

## Terminally sterilized solutions and suspensions

- Injectable solutions
- Nano-milled injectable suspensions
- Topical solutions and suspensions
- Eye drops

Our CDMO capabilities support your development program, from the clinic to market, with state-of-the-art manufacturing, analysis, and packaging of your ophthalmic therapeutic.

Our integrated, end-to-end services include translational development from preclinical to clinical, and beyond.

## Nonclinical/Preclinical Studies

- An on-site, boarded (DACVO) veterinary ophthalmologist
- Gene therapy ocular studies with Dutch belted rabbits

## Other capabilities

- Expertise in dosing different routes of administration
- Advanced ocular equipment at our clinical pharmacology sites
- Availability of ocular matrices for bioanalytical support

## Clinical studies

- Co-located ophthalmic center, located in the same building as one of our clinical pharmacology units
- Board-certified ophthalmologist as principal investigator
- In-house regulatory team with vast expertise in regulatory requirements for ophthalmic drug development

# ALTASCIENCES' RESOURCES

## Webinars and Podcasts

Advantages of Terminal Sterilization Over Aseptic Manufacturing

Gene and Cell Therapy: Enhanced CNS and Ocular Delivery in Nonhuman Primates—Overcoming Technical Challenges

Consultant Series: Nonclinical Considerations When Developing an Ophthalmic Drug

## Videos

Altasciences' Drug Development and Manufacturing Services

Virtual Tour of Altasciences' CDMO Facility

A Truly Integrated CRO/CDMO

## Webpage

Comprehensive Ophthalmic Drug Development Solutions

## Scientific Journal and Posters

*The Altascientist*—The Complexities of Early-Phase Ophthalmic Drug Development

*In Vivo* and Histological Analysis of Focal Chorioretinal Defects in Dutch Belted Rabbits

Evaluation of Formulation pH Tolerability in New Zealand White and Dutch Belted Rabbits Post-Intravitreal Administration

## Fact Sheet and eBooks

Ophthalmology Drug Development Solutions

Safety Assessment for Ophthalmic Products

End-to-End Ocular Drug Development Services

# ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 30 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.

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