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BY ELECTRONIC SUBMISSION

Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

CITIZEN PETITION

Bausch+Lomb submits this Citizen Petition pursuant to the Food and Drug Administration’s (“FDA”) regulations set forth at 21 C.F.R. §§ 10.30 and 10.31 and the Federal Food, Drug, and Cosmetic Act (“FDC Act”). Bausch+Lomb is the sponsor of Xipere (triamcinolone acetonide injectable suspension), for suprachoroidal use, indicated for the treatment of macular edema associated with uveitis. For the reasons discussed herein, Bausch+Lomb requests that FDA refuse to receive and/or refuse to approve any Abbreviated New Drug Application (“ANDA”) referencing Xipere that uses a different SCS injector than the approved proprietary SCS Microinjector unless that submission includes *in vivo* studies with clinical endpoints demonstrating that the product as a whole has the same safety and efficacy profile as Xipere. While Bausch+Lomb is aware of and appreciates the draft Product Specific Guidance (“PSG”) that FDA issued in February 2023 pertaining to this very issue, respectfully, Bausch+Lomb is concerned that the draft PSG does not go far enough.

As explained below, Xipere utilizes a novel route of administration that can be executed safely and effectively only with the injector approved in the Xipere New Drug Application (“NDA”), the SCS Microinjector. The marketing of a substitutable version of this drug product without the same injector introduces serious safety and efficacy risks. For example, use of a different unapproved injector in the suprachoroidal space risks hemorrhage, vision loss, and drug-related toxicities, which are safety concerns that are unquantifiable without studies involving the new injector. The same concerns apply to efficacy: Absent the SCS Microinjector, designed specifically to enhance bioavailability at diseased tissue, a similar efficacy profile cannot be ensured without assessment through clinical studies.

Given that any differences in the injector would change the safety and efficacy balance so significantly, it follows that additional studies should be necessary with

the introduction of a different delivery device. Consequently, FDA should refuse to receive or approve any ANDAs that include a differing injector, as the resulting product would not be “sufficiently similar to the device used to deliver the [Reference Listed Drug (‘RLD’)].”¹ To that end, and to address these concerns, Bausch+Lomb requests that FDA revise its draft PSG to require either use of the same injector as the RLD or to require *in vivo* studies demonstrating comparable safety and efficacy of a proposed injector, as well as the safety and efficacy of a switch between injectors upon automatic substitution. Additionally, Bausch+Lomb requests that FDA revise the draft PSG to include syringeability and glide force as additional physicochemical characteristics of the formulation for which comparison is recommended.

I. Actions Requested

Bausch+Lomb respectfully requests that FDA:

- Refuse to receive or approve any ANDA relying on Xipere as the RLD if that ANDA uses a different injector unless that submission includes *in vivo* and switching studies demonstrating the safety and efficacy of the product;
- Revise its recent draft PSG to require the same; and
- Revise the recent draft PSG to include syringeability and glide force as physicochemical characteristics required for comparative purposes.

II. Statement of Grounds

A. Legal Background

As modified by the Drug Price Competition and Patent Term Restoration Act of 1984 (the “Hatch-Waxman Act” or “Hatch-Waxman”),² the FDC Act seeks to balance innovation and patient access to affordable medicines by stimulating price-reducing generic competition.³ To that end, the Hatch-Waxman Act provides an abbreviated pathway to approval based on the Agency’s findings of safety and efficacy for a previously approved drug product (the “reference listed drug” or “RLD”): An ANDA under section 505(j) of the FDC Act. Under the ANDA pathway, FDA may approve a copy of the RLD based on data demonstrating that the

¹ FDA, Guidance for Industry: ANDA Submissions—Refuse-to-Receive Standards, Rev. 2, at 17 (Dec. 2016) [hereinafter “Refuse-to-Receive Guidance”].

² Pub. L. No. 98-417, 98 Stat. 1585 (1984).

³ *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1326 (D.C. Cir. 1998) (citing, *inter alia*, H.R. Rep. No. 98-857, pt. 1, at 14 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647).

proposed drug product and the RLD share the same active ingredient(s) in the same dosage form, use the same route of administration, are identical in strength or concentration, and are bioequivalent.⁴ Where these “sameness” requirements are satisfied, ANDA applicants need not replicate the RLD holder’s prior clinical trials because two materially indistinguishable drug products can be expected to have “the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.”⁵

When an ANDA is submitted, FDA makes a threshold determination as to whether it is substantially complete to permit Agency review.⁶ FDA regulations direct the Agency to “refuse-to-receive” an ANDA when that ANDA is not substantially complete.⁷ A “substantially complete” ANDA is one that, “on its face is sufficiently complete to permit a substantive review,” including all of the information required by section 505(j)(2)(A) of the FDC Act.⁸ FDA regulations detail the requirements for each ANDA under 21 C.F.R. § 314.94, and, in some instances, include by reference requirements set forth in 21 C.F.R. § 314.50. Necessary and recommended bioequivalence studies pertaining to specific products are set forth in individual PSGs; any deviations must be supported by “adequate justification.”⁹ Should the ANDA fail to include such recommended bioequivalence studies, an acceptable justification, or any of the other elements required under section 505(j) of the FDC Act or its implementing regulations, FDA will refuse-to-receive the ANDA.¹⁰ Additionally, relevant here, drug products intended for ophthalmic use must include information to show that the proposed product contains the same inactive ingredients in the same concentration as the RLD—or that the product is Q1/Q2 the same as the RLD—or FDA will refuse-to-receive the ANDA.¹¹

After “receiving” an ANDA, FDA then performs a substantive review. FDA must approve an ANDA unless it contains insufficient information to assure that the proposed drug product is both as safe as and as effective as its RLD.¹² Among other things, FDA reviews the application to evaluate whether the ANDA is sufficient to show that each proposed condition of use has previously been approved for the RLD; the active ingredient is the same as that of the RLD; the route of administration, dosage form, and strength is the same as the RLD; the proposed product is bioequivalent to the RLD; and the proposed labeling is the same as the RLD.¹³

⁴ 21 U.S.C. § 355(j)(2)(A).

⁵ 21 C.F.R. § 314.3.

⁶ 21 C.F.R. § 314.101(b)(1).

⁷ *Id.*

⁸ 21 C.F.R. § 314.3.

⁹ Refuse-to-Receive Guidance, at 14-15.

¹⁰ 21 C.F.R. § 314.3(d)(3).

¹¹ 21 C.F.R. § 314.94(a)(9)(iv).

¹² See generally 21 U.S.C. § 355(j)(4); 21 C.F.R. § 314.127.

¹³ *Id.*

Labeling, however, may differ to the extent that those differences arise due to changes arising from a petition filed under 21 C.F.R. § 314.93 or because the drug product and the RLD are produced or distributed by different manufacturers, including any aspect of labeling protected by patent.¹⁴

1. Bioequivalence

Under the FDC Act and FDA's implementing regulations, in order for FDA to approve an ANDA for a proposed generic version of a brand-name drug product, the application must contain, among other things, information showing that the proposed generic drug product is "bioequivalent" to the drug identified in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") as the RLD.¹⁵ A generic drug product is bioequivalent to the RLD if "the rate and extent of absorption of the drug [the "bioavailability"] do not show a significant difference from the rate and extent of absorption of the [RLD] when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses."¹⁶

The purpose of demonstrating bioequivalence is to determine whether changes in a proposed drug product's formulation or manufacturing will affect the rate or extent to which the active ingredient reaches the primary site of action. It is presumed that a drug product containing the identical active ingredient will behave in the same way as the RLD if it reaches the primary site of action at the same rate and to the same extent as the RLD.¹⁷ Thus, ANDA applicants must conduct bioequivalence and bioavailability testing using the most accurate, sensitive, and reproducible approach available.¹⁸ Such methods include comparative pharmacokinetic testing ("PK"), *in vitro* tests predictive of human *in vivo* bioavailability, clinical endpoint testing, and other *in vitro* studies.

Although PK studies are the preferred method for demonstrating bioequivalence, such studies are feasible only for drugs intended to be absorbed systemically. For locally-acting drugs that are not intended to be absorbed systemically, FDA recognizes that "[w]ell-controlled clinical trials that establish the safety and effectiveness of the drug product . . . or appropriately designed comparative clinical trials" both "for purposes of demonstrating bioequivalence" may be "sufficiently accurate for measuring bioavailability or demonstrating

¹⁴ 21 C.F.R. § 314.94(a)(8)(iv).

¹⁵ See FDC Act §§ 505(j)(2)(A)(iv), 505(j)(4)(F); 21 C.F.R. §§ 314.94(a)(7), 314.127(a)(6)(i).

¹⁶ FDC Act § 505(j)(8)(B)(i).

¹⁷ See 21 C.F.R. § 320.1(e).

¹⁸ 21 C.F.R. § 320.24.

bioequivalence of dosage forms intended to deliver the active moiety locally. . . .”¹⁹ Indeed, comparative clinical trials are particularly suitable for “dosage forms intended to deliver the active moiety locally, forms that are not intended to be absorbed, or drug products for which traditional pharmacokinetic studies are not feasible.”²⁰ This is because most locally acting drugs do not produce measurable concentrations in blood or plasma, and in those that do, the drug concentration in such fluids rarely, if ever, correlates to concentration at the actual site of drug action.²¹

Though not all generic products are required to have the same inactive ingredients as their reference products, FDA does require certain generic products to have the same inactive ingredients as the RLD. In particular, FDA will refuse to approve an ANDA for a parenteral, ophthalmic, or otic drug that is not “quantitatively” and “qualitatively” the same—i.e., has the same ingredients in the same concentration—as its reference products with exceptions for preservatives, buffers, or antioxidants.²² In these circumstances, FDA will consider an inactive ingredient in, or the composition of, a proposed generic ophthalmic drug “unsafe” and will refuse to approve the ANDA if the drug does not contain the same inactive ingredients in the same concentration as the RLD and/or if the applicant fails to demonstrate that any allowable difference does not affect the safety or efficacy of the proposed product.²³

2. Combination Product ANDAs

The ANDA pathway may be used for abbreviated approval of combination products so long as the “sameness” requirements can be met for the entire product. For a drug-device combination product, FDA will Refuse-to-Receive the ANDA “if a device used to deliver the drug is not sufficiently similar to the device used to deliver the RLD.”²⁴ Such a device must be “similar enough” to “ensure that its performance characteristics, operating principles, and critical design attributes will result in a product that will perform the same as the RLD under the conditions of use described in the labeling”—even if the design is not the same.²⁵ While “[s]ome design differences may be acceptable,” that is so *only* “as long as they do not significantly alter product performance or operating principles and do not result in impermissible

¹⁹ *Id.* at (b)(4).

²⁰ FDA, MAPP 5210.4 Rev. 3, at 5 (May 2023).

²¹ FDA, Draft Guidance for Industry: Topical Dermatological Drug Product NDAs and ANDAs - In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies 3 (June 1998).

²² 21 C.F.R. § 314.94(a)(9).

²³ 21 C.F.R. § 314.22(b)(1).

²⁴ Refuse-to-Receive Guidance, at 17.

²⁵ *Id.*

differences in labeling.”²⁶ Thus, a generic and its RLD need not be identical as long as differences do not require testing that would preclude approval under ANDA or result in labeling differences that are too dissimilar.²⁷

Though a proposed generic combination product need not be identical to the RLD in all respects, as an identical design may not always be feasible, a product is eligible for submission as an ANDA only if it will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.²⁸ FDA considers “whether the generic combination product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the generic combination product.”²⁹ To that end, the Agency’s review process assesses both the drug product as a whole and its individual components for the introduction of new risks, including both risks intrinsic to the new product and risk associated with switching from one product to the other without additional training.³⁰

B. Factual Background

Uveitis is a general term used to describe a set of approximately 30 ocular inflammatory diseases and is a leading cause of visual loss in the U.S.³¹ Uveitis may affect multiple anatomic locations in the eye, including the anterior, intermediate, and/or posterior.³² Visual loss associated with uveitis arises from, among other conditions, macular edema, which “is defined as abnormal thickening of the macula associated with the accumulation of fluid in the outer plexiform and the inner nuclear layers of the retina . . .”³³

Macular edema is characterized by blurry or wavy vision.³⁴ Treatment for the condition typically addresses the underlying cause.³⁵ Where that underlying cause is

²⁶ FDA, Response to Citizen Petition from King Pharmaceuticals, Docket No. FDA-2009-P-0040, at 6 (July 29, 2009) [hereinafter “King Petition”].

²⁷ FDA, Draft Guidance for Industry: Comparative Analyses and Related Comparative Use Human Factors for Drug-Device Combination Product Submitted in an ANDA, at 5 (Jan. 2017) [hereinafter “Combination Product Guidance”].

²⁸ *Id.* at 2-3.

²⁹ *Id.* at 3.

³⁰ King Petition, *supra* n.26, at 6.

³¹ Xipere, NDA 211950, Cross-Discipline Team Leader Review, at 2 (Oct. 17, 2019) (“CDTL 2019”).

³² *Id.*

³³ *Id.*

³⁴ NIH, National Eye Institute, Macular Edema (Aug. 5, 2022), <https://tinyurl.com/MacularEdema> (last visited Oct. 12, 2023).

³⁵ Daniel Porter, American Academy of Ophthalmology, What Is Macular Edema (Apr. 27, 2023), <https://tinyurl.com/AAOMacularEdema> (last visited Oct. 12, 2023).

inflammation, like with uveitis, corticosteroid treatment—whether through topical, oral, or injectable administration—is the standard of care.³⁶ Such corticosteroids include triamcinolone acetonide, which has been considered safe and effective for use in the treatment of certain types of uveitis for more than 50 years.³⁷

1. Early Triamcinolone Acetonide Products

As part of the Drug Efficacy Study Implementation (“DESI”) review, FDA determined in the 1970s that triamcinolone acetonide, available in multiple routes of administration, is an efficacious anti-inflammatory agent for the treatment of certain types of uveitis.³⁸ FDA first approved several versions of triamcinolone in 1957 for intramuscular and intra-articular use followed by several other versions for multiple indications in the 1960s and 1970s.³⁹ These products, Kenalog and its derivatives Kenalog-10 and Kenalog-40, served as the RLD for several follow-on triamcinolone products. Currently, there are approximately one hundred versions of triamcinolone acetonide on the market; most are approved for intramuscular, intra-articular, and oral administration, but FDA has approved two products administered through intravitreal injection, including an injectable approved in 2007 called Triesence for the treatment of ophthalmic diseases.

Given its widespread use, it is no surprise that FDA has already issued multiple PSG documents related to triamcinolone acetonide. Two of those PSGs provide recommendations for injectable options—one for intravitreal injections referencing Triesence (NDA 022048) and one for injections referencing Kenalog-10 and Kenalog-40 (NDAs 012041 and 014901).⁴⁰ In both of these PSGs, FDA recommends use of an *in vitro* option for bioequivalence testing for any proposed ANDAs referencing these products. Specifically, each PSG for injectable triamcinolone acetonide allows for *in vitro* testing when the test product and the RLD product are Q1/Q2 the same and physicochemical characterizations of the test and reference products demonstrate sameness in:

- Polymorphic form of triamcinolone acetonide;

³⁶ *Id.*

³⁷ 37 Fed. Reg. 3,775, 3,775 (Feb. 19, 1972) (finding triamcinolone effective in the treatment of inflammatory ophthalmic diseases including “[d]iffuse posterior uveitis and choroiditis”).

³⁸ CDTL 2019, at 2.

³⁹ NDA 211950, Cross-Discipline Team Leader Review of Resubmission, at 5 (Oct. 20, 2021) [hereinafter “CDTL 2021”]; NDA 22048, Office Director Memo, at 2-3 (Nov. 29, 2007); NDA 22048, Medical Review, at 14 (Nov. 27, 2007).

⁴⁰ FDA, Product Specific Guidance (“PSG”), Triamcinolone Acetonide Intravitreal Injection, NDA 022048 (July 2018); FDA, PSG, Triamcinolone Acetonide Injectable Injection, NDAs 012041 and 014901 (rev. Nov. 2021).

- Crystalline shape and morphology;
- Appearance, pH, osmolality, viscosity over range of shear rates, specific gravity;
- Soluble fraction in final drug product; and
- Particle size and size distribution.

Additionally, the PSG require comparative *in vitro* drug release tests that discriminate the effect of process variability in the product of the test formulation.⁴¹ The PSG for the triamcinolone injection also provides an *in vivo* option: A bioequivalence study with PK endpoints. Notably, neither of these triamcinolone injectable products is distributed with or labeled for use with a specific injector, and thus neither PSG includes a requirement for comparable device components.

FDA also has published PSGs for triamcinolone acetonide presented as drug and device combination products.⁴² One of those PSGs is for a proposed triamcinolone acetonide nasal inhaler referencing Nasacort (triamcinolone acetonide) nasal spray, which is an Over-the-Counter product distributed in a metered nasal inhaler. That PSG offers putative generic applicants an option between eight *in vitro* bioequivalence studies or six *in vitro* bioequivalence studies with one *in vivo* study with PK endpoints and one comparative clinical endpoint study. The *in vitro* option requires Q1/Q2 sameness and mandates testing of the drug product using the final device configuration to compare single actuation content, droplet size distribution, drug in small particles, spray pattern, plume geometry, prime and repriming, drug particle size distribution, and dissolution.⁴³ Alternatively, if the product is not Q1/Q2 the same, sponsors could submit six *in vitro* studies using the final device to compare single actuation content, droplet size distribution, drug in small particles, spray pattern, plume geometry, prime and repriming.⁴⁴ The *in vivo* studies look at the required endpoints after use of the entire product. In other words, the PSG for the approved triamcinolone acetonide nasal spray combination product requires evaluation of both the formulation *and* the device as compared to the RLD.⁴⁵

FDA also has published a PSG for an extended-release intra-articular triamcinolone acetonide suspension product, which is presented as a co-packaged kit containing a vial of the drug in powder form, a vial of diluent, and a sterile vial adapter device constituent.⁴⁶ The PSG, citing NDA 208845 as the RLD, requires one *in vitro* bioequivalence study on drug release to detect formulation differences, one *in vivo* bioequivalence study with PK endpoints, and supportive comparative

⁴¹ *Id.*

⁴² FDA, PSG, Triamcinolone Acetonide Nasal Spray, NDA 020468 (rev. Aug. 2023).

⁴³ *Id.*

⁴⁴ *Id.*

⁴⁵ *Id.*

⁴⁶ FDA, PSG, Triamcinolone Acetonide Intra-Articular, NDA 208845 (Nov. 2022).

characterization studies.⁴⁷ The PSG also recommends that applicants consider “the size and shape, the external critical design attributes, and the external operating principles of the RLD device” and include “complete comparative analyses” so FDA can determine 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.”⁴⁸ Notably, the vial adapter device component “is used in several other drug products,” is not a novel device, and is familiar to most healthcare providers.⁴⁹

2. Xipere (triamcinolone acetonide injectable suspension), for suprachoroidal use.

While triamcinolone acetonide has been used widely for years, FDA, for the first time in October 2021, approved a triamcinolone acetonide injectable suspension drug and device combination product, Xipere, intended for use in the suprachoroidal space of the eye. Xipere is a corticosteroid indicated for the treatment of macular edema associated with uveitis that consists of a novel device called the SCS Microinjector and a formulation composed specifically for use with the injector.⁵⁰ Notably, Xipere is the first product *ever* FDA-approved for use in the suprachoroidal space.

Xipere was submitted by Clearside Biomedical, Inc., approved under NDA 211950, and subsequently licensed by Bausch+Lomb. As a 505(b)(2) NDA, Xipere’s approval relied on FDA’s findings of safety and efficacy for Kenalog (triamcinolone acetonide) injection, approved under NDA 14901, as well as a 6-month, randomized, multicenter, double-masked, sham-controlled clinical study assessing improvement in best corrected visual acuity in patients with macular edema associated with anterior, intermediate, posterior, or pan uveitis.⁵¹ The trial established the safety and effectiveness of triamcinolone acetonide as delivered by the SCS Microinjector into the anatomically-complex suprachoroidal space.⁵²

Xipere’s SCS Microinjector is the first of its kind. Designed specifically for precise delivery of medication into the suprachoroidal space, the SCS Microinjector is comprised of a proprietary manual piston syringe and two needle assemblies available in 900-μm and 1100-μm needle length.⁵³ The SCS Microinjector should be used exactly in accordance with its instructions: It is placed approximately 4 mm posterior

⁴⁷ *Id.*

⁴⁸ *Id.* at 2-3.

⁴⁹ NDA 208845, Cross Discipline Peer Review, at 3-4 (Oct. 6, 2017).

⁵⁰ NDA 211950, Xipere Full Prescribing Information § 3 (2021).

⁵¹ *Id.* at § 14.

⁵² CDTL 2019, at 2.

⁵³ *Id.*; CDTL 2021, at 2.

to the limbus, and once the microneedle penetrates the sclera to reach the suprachoroidal space, the triamcinolone acetonide formulation is released through the open bevel of the needle, which then spreads to the back of the eye.⁵⁴ Because of the design of the SCS Microinjector and living eye fluid flow dynamics, the injectate moves posteriorly from the site of the injection upon administration, and, as the suprachoroidal space expands to accommodate fluid transport, the fluid is absorbed into the inner sclera, choroid, retinal pigment epithelial cells, and retina.⁵⁵ The placement in the suprachoroidal space allows the delivery of targeted therapy to the posterior structures of the eyes while preventing the drug from spreading to other tissues, like the anterior chamber and vitreous.⁵⁶

Because access to the suprachoroidal space is delicate, no safe and reliable device has been FDA-approved to deliver medicament to the space before Xipere. While the SCS Microinjector designed for use with Xipere safely and adequately delivers medicament into the suprachoroidal space, FDA had no experience with this type of device and suprachoroidal delivery during Xipere’s NDA review. Thus, the Agency required Clearside to submit for approval purposes clinical studies establishing both that the delivery of triamcinolone acetonide to the back of the eye would effectively treat macular edema associated with uveitis and that the SCS Microinjector could reliably deliver the medicament to the back of the eye.⁵⁷ To support approval, Clearside performed hundreds of injections in various trials submitted to the Agency.⁵⁸ However, not all trial injections used the SCS Microinjector: Some used a similar injector with all the same critical features and attributes. Notwithstanding their similarities, FDA required Clearside to conduct additional testing using the final, to-be-marketed SCS Microinjector, and using the final, to-be-marketed SCS Microinjector, Clearside submitted additional data from 225 injections performed in 173 patients.⁵⁹ FDA separately examined these data to assess both the safety and efficacy of the triamcinolone acetonide formulation *and* the precise characteristics of the device used for delivery.⁶⁰

Proper use of the SCS Microinjector is critical to the safe delivery of Xipere into the suprachoroidal space. It is for this reason that one-third of the Xipere Prescribing Information is dedicated to the proper use of the injector and that

⁵⁴ NDA 211950, Xipere Full Prescribing Information § 2.3 (2021).

⁵⁵ CDTL 2021, at 2; Bryce Chiang et al., The suprachoroidal space as a route of administration to the posterior segment of the eye, 126 Adv. Drug. Delivery Rev. 58, § 2.3 (2018) [hereinafter “Chiang (2018)”] (Exhibit 1); Kozuyuki Emi et al., Hydrostatic Pressure of the Suprachoroidal Space, 30 Investig. Ophthalmol. Vis. Sci. 233, 238 (1989) (Exhibit 2).

⁵⁶ Chiang (2018), *supra* n.55, at § 3.2.

⁵⁷ CDTL 2021, at 20.

⁵⁸ *Id.*

⁵⁹ *Id.*

⁶⁰ *Id.*

Bausch+Lomb offers extensive training on the proper procedure to use the SCS Microinjector. As part of that training, Bausch+Lomb provides a kit including a practice microinjector and needle assemblies, a synthetic eye for injection practice, and step-by-step use instructions.

Importantly, the formulation of the drug component included in Xipere was developed specifically for use with the SCS Microinjector; extensive testing and development found that the formulation is critical to its proper functioning of the device component. That formulation, including the particle size distribution and surfactant, was optimized to minimize variability in the use of the microinjector. This was assessed preclinically in animal models, followed by clinical use assessments, which demonstrated that Xipere was superior to intravitreal triamcinolone acetonide (Triesence) with respect to these features.⁶¹ Furthermore, optimization of the formulation specifically for and concurrently with the SCS Microinjector enhanced operator tactile feedback for loss of resistance, a key localization and safety feature in microneedle-based SCS injection.⁶² Collectively, these features go to the “syringeability” and glide force of the product—characteristics that are essential to the proper functioning of the SCS Microinjector.

3. Xipere as an RLD

Currently there are no approved products referencing Xipere. To encourage competition from follow-on products, FDA, in February 2023, published a draft PSG laying out bioequivalence testing recommendations for any putative sponsor of an ANDA referencing Xipere (triamcinolone acetonide) injectable suspension.⁶³ That draft PSG recommends only *in vitro* options for bioequivalence testing. Specifically, this draft PSG recommends two *in vitro* bioequivalence studies with supporting characterization studies so long as the follow-on formulation is Q1/Q2 the same as Xipere and the sponsor demonstrates “[a]cceptable comparative physicochemical characterization” to Xipere.⁶⁴ Similar to the intravitreal and injectable triamcinolone PSGs, the injectable suspension draft PSG recommends comparative studies of:

- Polymorphic form of triamcinolone acetonide;
- Crystalline shape and morphology; and

⁶¹ Leroy Muya et al., Suprachoroidal Injection of Triamcinolone Acetonide Suspension: Ocular Pharmacokinetics and Distribution in Rabbits Demonstrates High and Durable Levels in the Chorioretina, 38 J. Ocul. Pharmacol. Ther. 459, 465 (2022) [hereinafter “Muya (2022)”] (Exhibit 3).

⁶² *Id.*

⁶³ FDA, PSG, Triamcinolone Acetonide Suspension Injection, NDA 211950 (Feb. 2023).

⁶⁴ *Id.* at 1.

- Appearance, pH, osmolality, specific gravity, soluble fraction of triamcinolone acetonide, sedimentation rate and volume, and viscosity over a range of shear rates.⁶⁵

If these physicochemical qualities are comparable, FDA recommends only drug particle size and size distribution *in vitro* bioequivalence studies and comparative *in vitro* drug release of triamcinolone acetonide bioequivalence studies. FDA, however, requests no comparison between the reference product and the proposed product with respect to two critical factors: glide force or syringeability.

The draft PSG does request additional comparative information between the proposed device component and the SCS Microinjector, but that request is limited. The draft PSG explains that the SCS Microinjector is equipped with three parts—the syringe, vial adapter, and needles—and recommends that applicants *examine* the size and shape, external critical design attributes, and external operating principles of the device when designing the proposed follow-on product. The draft PSG, however, stops short of recommending any testing of device specifications or *in vivo* testing using the proposed follow-on injector to ensure comparability—and safety and effectiveness—of the device.

C. FDA Should Refuse to Receive or Approve Any ANDA That Does Not Include the Same Microinjector as the RLD.

While the ophthalmic use of triamcinolone acetonide is not new, Xipere utilizes a new route of administration—and the first delivery device capable of such route of administration; for that reason, FDA’s findings of safety and efficacy hinge neither on the formulation nor on the device but on the use of both together.⁶⁶ Indeed, unlike intravitreal triamcinolone acetonide, which can be used with any off-the-shelf needle, the Xipere product includes a specific delivery device—the SCS Microinjector—that has undergone rigorous testing for safety and efficacy *with* the Xipere formulation. In other words, FDA’s findings of safety and efficacy for Xipere consider the entirety of the *drug product*—including the delivery device—as a unit.⁶⁷ And it is for that reason that FDA required Clearside to conduct additional studies—

⁶⁵ *Id.*

⁶⁶ CDTL 2021, at 3 (Xipere “provides an effective alternative route of administration negating the need for entering the vitreous.”); NDA 211950, Medical Officer’s Review Class 2 Resubmission, at 1 (Aug. 2, 2021) (explaining that additional testing is needed with the “final to-be-marketed SCS Microinjector Delivery System” because, without it, “[t]here is insufficient information about the drug product to determine whether the product is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling.”).

⁶⁷ *Id.*

not just with a *version* of the delivery device but with the *final, to-be-marketed* SCS Microinjector—to ensure that it was as safe and effective as the prior version.

Though FDA has long taken the position that ANDA products need not be identical to their RLDs in all respects, that holds true only where the proposed changes do not raise additional questions of safety and efficacy.⁶⁸ Indeed, “[t]he Agency’s review process for ANDAs for combination products considers whether any difference in materials, design, or operating principles introduces a new risk” considering both “the RLD as a whole and its individual constituent parts.”⁶⁹ Here, the delivery device component is integral to the safety and efficacy of the drug product because FDA’s assessment of the risks of the product were based on the specific SCS Microinjector’s ability to deposit triamcinolone acetonide into the suprachoroidal space.⁷⁰ Given the tandem development and review of the drug and device components, FDA’s findings of safety and efficacy can be extrapolated only when both components—not just the triamcinolone formulation—are the same. Any differences in the device risks differences in formulation delivery, which is integral to the therapeutic effect of the drug product as a whole.⁷¹ While some design differences may be acceptable, this is so only “as long as [such differences] do not significantly alter product performance or operating principles . . .”⁷² The absence of such differences cannot be assumed without testing where the follow-on device is novel, as more complete information about the novel follow-on device is necessary to demonstrate that the product will “perform the same as the RLD.”⁷³

With little experience with the SCS Microinjector and no experience reviewing other types of microinjectors, FDA should require any ANDA referencing

⁶⁸ King Petition, *supra* n.26, at 6.

⁶⁹ *Id.*

⁷⁰ See NDA 211950, Medical Officer’s Review Class 2 Resubmission, *supra* n.66; NDA 211950, Clinical Review, at 18 (Oct. 16, 2019) (“The pivotal study PEACHTREE (CLS1001-301) was a Phase 3, randomized, masked, sham-controlled, multicenter *study to assess the efficacy and safety of suprachoroidally injected CLS-TA (4 mg) administered . . .*”) (emphasis added); *id.* at 42 (“The safety of triamcinolone via routes other than suprachoroidal has been well established based on the long history of the use of this product and the extensive safety database. This review will concentrate on evaluating any potential increased or unknown *risk associated with this product administered by this new route* in uveitis patients with macula edema.”) (emphasis added).

⁷¹ See e.g., Viral Kansara et al., Suprachoroidal delivery enables targeting, localization and durability of small molecule suspensions, 349 J. Control. Release 1045, 1047 (2022) [hereinafter “Kansara (2022)’] (“The performance of the microinjector is impacted by the characteristics of the injectate. The role of injectate viscosity, injection volume, and particle size on the spread and coverage of injectate into the SCS, and durability has been elucidated in preclinical studies”) (Exhibit 4).

⁷² King Petition, *supra* n.26, at 6.

⁷³ *Id.*

Xipere to use the same injector unless the ANDA includes *in vivo* studies with clinical endpoints to demonstrate that any injector that is not the SCS Microinjector delivers the formulation into the suprachoroidal space as well as the SCS Microinjector does.

Switching studies to show that the new injector can be substituted for the SCS Microinjector should also be requested. These tests are necessary to ensure that the “product that will perform the same as the RLD under the conditions of use described in the labeling.”⁷⁴ And, because the submission of *in vivo* clinical studies evaluating both the safety and efficacy of triamcinolone acetonide used with the new injector and the risks of switching injectors are necessary to ensure that the proposed injector is “sufficiently similar to the device used to deliver the RLD,” FDA should Refuse-to-Receive any ANDA omitting these studies.⁷⁵ Should these studies fail to demonstrate that the new product and its new injector can be substituted for the RLD, FDA should refuse to approve the ANDA in the interest of patient safety and efficacy.⁷⁶

1. The drug delivery device is critical to FDA’s findings of safety and efficacy.

FDA approved Xipere as a combination product with its functionality coming not just from the drug component but also from the device. Without the notable innovation of the SCS Microinjector, there are no assurances that the drug will successfully—and safely—reach the suprachoroidal space. For that reason, the same risk profile cannot be extrapolated to an ANDA referencing Xipere as an RLD with a different injector. An off-the-shelf needle, or even a custom but new needle, brings into question variables such as material, gauge, inner diameter, length, plunger aspiration and depression forces, dispensability, and functionality.⁷⁷ Differences in delivery device components therefore inherently raise questions that are not addressed in FDA’s Xipere findings. Those findings, absent data for the differing proposed device, cannot be relied upon for approval of an ANDA referencing Xipere.

As noted, triamcinolone acetonide has been used safely and effectively as an ophthalmic treatment for more than 50 years, and thus the risk profile of triamcinolone acetonide as an active agent was never in doubt. Accordingly, FDA did not require clinical trials assessing the safety and efficacy of triamcinolone for the

⁷⁴ Refuse-to-Receive Guidance, at 17.

⁷⁵ See *id.* (explaining that FDA would Refuse-to-Receive an ANDA “if a device used to deliver the drug is not sufficiently similar to the device used to deliver the RLD.”).

⁷⁶ See King Petition, *supra* n.26, at 6 (noting that FDA considers “whether the generic combination product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the generic combination product.”).

⁷⁷ NDA 211950, Product Quality Review, at 6 (Apr. 22, 2021).

treatment of uveitis. Nonetheless, FDA *did* require clinical studies for approval of Xipere, and those studies looked specifically at the safety and efficacy of the delivery of triamcinolone acetonide into the suprachoroidal space by way of the SCS Microinjector. Indeed, by all accounts, the pivotal study, PEACHTREE, was “a Phase 3, randomized, masked, sham-controlled, multicenter study *to assess the efficacy and safety of suprachoroidally injected CLS-TA (4 mg)* administered compared to control (sham procedure to mimic a suprachoroidal injection) in the treatment of subjects with macular edema (ME) associated with uveitis.”⁷⁸ In other words, FDA already knew that triamcinolone acetonide could effectively address uveitis, so its findings of safety and efficacy are based *only* on the deposit of triamcinolone acetonide into the suprachoroidal space using the SCS Microinjector.⁷⁹ Use of any injector that is not the same as the SCS Microinjector is not contemplated by such findings.

In fact, the specific SCS Microinjector for use in Xipere was so important to FDA’s assessment of the product’s risk profile that the Agency questioned whether data using an earlier version of the SCS Microinjector—one that is fundamentally the same as the final version in all critical ways—were sufficiently representative of the risks involved with using the “final to-be-marketed SCS Microinjector.”⁸⁰ Though Clearside performed hundreds of suprachoroidal injections with an earlier model of the injector that was identical to the SCS Microinjector in terms of internal volumes, surface areas, lengths, and weights of all components, FDA nevertheless required additional studies using the “final to-be-marketed SCS Microinjector.” In turn, FDA separately reviewed an additional 225 injections in 173 patients using the final to-be-marketed SCS Microinjector to make its approval decision.⁸¹

FDA’s concerns about the extrapolation of clinical study data to the use of the product with the new microinjector model—notwithstanding the fact that all of the “components of the SCS injector and the final to-be-marketed SCS Microinjector coming into direct contact with the drug, as well as the internal volumes, surface areas, lengths, and weights of all components (i.e., syringe and needles) were identical” and device instructions for administration remained the same—highlight the criticality of the device design.⁸² The same concerns FDA raised in the Xipere

⁷⁸ NDA 211950, Clinical Review, at 18 (Aug. 1, 2019) (emphasis added).

⁷⁹ See *id.* at 7.

⁸⁰ Such ways include internal volumes, surface areas, lengths, and weights of all components. NDA 211950, Medical Officer’s Review Class 2 Resubmission, at 3 (Aug. 2, 2021). Other attributes that are critical to the injector include essential performance requirements for the Microinjector, including volume delivered, plunger depression force, plunger aspiration force, needle length, vial adapter insertion force, and needle cap distance. NDA 211950, Intercenter Consult Memorandum, at 5 (Oct. 18, 2021).

⁸¹ NDA 211950, Medical Officer’s Review Class 2 Resubmission, at 3 (Aug. 2, 2021).

⁸² *Id.*

review should only be magnified where a new applicant uses a totally new injector. Subjecting the SCS Microinjector to rigorous testing in its final form (i.e., the final to-be-marketed injector used with the final drug formulation) but recommending a mere comparison of device design features for a totally new, untested follow-on device would be inconsistent and illogical.

While Xipere is listed in FDA's Orange Book as an injectable suspension without reference to the suprachoroidal space, it is important to note that an injector specifically capable of delivering product to the suprachoroidal space is essential to the safety and risk profile of Xipere. The minimally invasive SCS Microinjector obviates the problems with other injections like intravitreal injections, which can be invasive and associated with hemorrhages, discomfort, retinal detachment, cataract formation, and bacterial endophthalmitis.⁸³ Intravitreal injection results in broad diffusion through the eye with potential for off-target effects.⁸⁴ Conversely, local delivery into the suprachoroidal space increases site specificity, thereby decreasing exposure of nontarget tissues to the drug.⁸⁵ This potentially limits and reduces side effects, including cataracts and increased intraocular pressure, while also minimizing rapid elimination of small molecule suspensions like Xipere.⁸⁶ Thus, Xipere's unique safety profile is dependent on this new route of administration.⁸⁷

But past experience demonstrates that this new route of administration—or the safe deposit into the suprachoroidal space—is a challenge: While there have been attempts to access the suprachoroidal space through means other than the SCS Microinjector, including delivery through a catheter or through a standard hypodermic needle, the required procedures are invasive and carry significant risk.⁸⁸ Indeed, any imprecise attempts to access the suprachoroidal space could lead to serious adverse events, such as retinal tears or detachments, significant pain, and

⁸³ Uma Do J.P. Rai et al., The suprachoroidal pathway: a new drug delivery route to the back of the eye, 20 Drug Discov. Today 491, 492 (2015) [hereinafter "Rai (2015)"] (Exhibit 5).

⁸⁴ Shelley E. Hancock et al., Biomechanics of suprachoroidal drug delivery: From benchtop to clinical investigation in ocular therapies, 18 Expert Opin. Drug Deliv. 777, 777 (2021) [hereinafter "Hancock (2021)"] (Exhibit 6).

⁸⁵ Rai (2015), *supra* n.83, at 495.

⁸⁶ *Id.*; Samirkumar R. Patel et al., Targeted Administration into the Suprachoroidal Space Using a Microneedle for Drug Delivery to the Posterior Segment of the Eye, 53 Investig. Ophthalmol. Vis. Sci. 4433, 4440 (2012) (Exhibit 7).

⁸⁷ NDA 211950, Clinical Review, at 42 (Oct. 16, 2019) ("The safety of triamcinolone via routes other than suprachoroidal has been well established based on the long history of the use of this product and the extensive safety database. This review will concentrate on evaluating any potential increased or unknown **risk associated with this product administered by this new route** in uveitis patients with macula edema.").

⁸⁸ Hancock (2021), *supra* n.84.

potential vision loss.⁸⁹ The improper introduction of a drug solution into the suprachoroidal space can result in rapid drug diffusion covering the entire suprachoroidal surface, which, in turn, can induce drug-related toxicities of the surrounding tissues.⁹⁰ This is why Clearside meticulously evaluated the safety and efficacy of the drug product (triamcinolone acetonide) and the SCS Microinjector in combination, preclinically and clinically, in order to demonstrate the transport of the drug product into the eye, delivered via the injector, does not result in drug-related toxicities.

Clearside selected a microneedle device like the SCS Microinjector to use with Xipere because it provides more reliable and less invasive access to the suprachoroidal space, allowing for more controlled and continuous drug release, as well as accurate placement into the suprachoroidal space.⁹¹ Such controlled release and accurate placement helps overcome rapid fluctuation of the dosed drugs into the suprachoroidal space thereby reducing toxicity to the surrounding tissues and reducing injury to the underlying retinal layers.⁹² Suprachoroidal space delivery supplies far less active ingredient to unwanted portions of the eye. This is reflected in the human PK studies submitted to the Xipere NDA, which showed that plasma triamcinolone acetonide concentrations consistently are below 100 pg/mL, “indicating that systemic exposure is negligible, and the drug is confined within the suprachoroidal space.”⁹³ Thus, FDA found, “there is limited absorption and distribution of the drug from its local site.”⁹⁴ Conversely, the mean peak plasma concentrations in an oral triamcinolone acetonide is 10,500 pg/mL, indicating systemic absorption and distribution.⁹⁵ And it is well known that a “key limitation of [intravitreal] administration is that drug exposure to unaffected ocular tissue s leads to drug-related off-target adverse effects.”⁹⁶

Effectiveness of Xipere is also inextricably linked to the SCS Microinjector.⁹⁷ While traditional ophthalmic routes of administration cannot target specific tissues,

⁸⁹ Rai (2015), *supra* n.83, at 495.

⁹⁰ *Id.*

⁹¹ *Id.*; Hancock (2021), *supra* n.84, at 779.

⁹² Rai (2015), *supra* n.83, at 495; Rachel R. Hartman & Uday B. Kompella, Intravitreal, Subretinal, and Suprachoroidal Injections: Evolution of Microneedles for Drug Delivery, 34 J. Ocul. Pharmacol. Ther. 141, 148 (2018) [hereinafter “Hartman (2018)”] (Exhibit 8).

⁹³ NDA 211950, Product Quality Review; Chapter VII: Biopharmaceutics, at 2 (Aug. 15, 2019).

⁹⁴ *Id.*

⁹⁵ *Id.*

⁹⁶ Muya (2022), *supra* n.61, at 464.

⁹⁷ Thomas Ciulla & Steven Yeh, Microinjection via the suprachoroidal space: a review of a novel mode of administration, 28 Am. J. Manag. Care S243, S244 (2022)

the SCS Microinjector created a method to provide precise, accurate, and controlled non-surgical targeted delivery to the affected tissue layers.⁹⁸ In turn, this targeted delivery allows for an increase in bioavailability at the diseased tissue, which allows the target tissues—the choroid and retina—to retain therapeutic levels of the drug.⁹⁹ The deposit of suspension into the suprachoroidal space is shown to last for at least 1-2 months, suggesting that the placement of medicament with the SCS Microinjector facilitates sustained delivery, as well as dose sparing.¹⁰⁰ By providing a delivery method that can maintain therapeutic levels of a drug in the choroid and retina, the SCS Microinjector enhances the efficacy profile of triamcinolone acetonide.¹⁰¹ Consequently, the SCS Microinjector is critical to the efficacy of Xipere; substitution with any other type of injector, absent clinical data, provides no assurances that a generic referencing Xipere would be as effective.

Given the importance of the SCS Microinjector to the risk profile of Xipere, any changes to it, as demonstrated by FDA’s required testing of the “final to-be-marketed device” in its review of Xipere, inherently changes the risk profile of the entire product.¹⁰² As of now, no other injector has been clinically shown to deliver a product reliably and safely into the suprachoroidal space, and certainly not as safely or as effectively as the SCS Microinjector. And while it is possible that a different injector could do so, this can be shown only through data. Therefore, should any ANDA applicant propose a new injector, FDA should require *in vivo* studies with clinical endpoints utilizing both the new injector and the relevant formulation to assess the safety and efficacy of the proposed injector as compared to a sham procedure to mimic a suprachoroidal injection, as Clearside performed in the PEACHTREE trial.¹⁰³

(“[Xipere] is the first FDA-approved treatment to utilize the SCS and is indicated for the treatment of UME”) (Exhibit 9).

⁹⁸ Chiang (2018), *supra* n.55, at § 6.

⁹⁹ Patel, *supra* n.86, at 4433; Kansara (2022), *supra* n.71, at 1048.

¹⁰⁰ Rai (2015), *supra* n.83, at 494.

¹⁰¹ Chen-rei Wan et al., Clinical Characterization of Suprachoroidal Injection Procedure Utilizing a Microinjector across Three Retinal Disorders, 9 *Transl. Vis. Sci. Technol.* 1, 6 (2020) [hereinafter “Wan (2020)”] (Exhibit 10).

¹⁰² NDA 211950, Medical Officer’s Review Class 2 Resubmission, *supra* n.66, at 42 (noting that the safety profile of triamcinolone is well-established and thus the review focuses on “any potential increased or unknown risk associated with this product administered by this new route in uveitis patients with macula edema” via the SCS Microinjector).

¹⁰³ NDA 211950, Clinical Review, at 18 (Aug. 1, 2019).

2. Any switch in injectors should not be done without additional training.

Successful use of the SCS Microinjector is inextricably tied to the detailed on-label instructions and extensive training offered by Bausch+Lomb since launch. Any product with a different injector, even if intended for use within the suprachoroidal space, raises concerns as to the relevance and applicability of that training. Though the Xipere training is not mandatory, most practitioners take advantage of it. Changes to the device would obviate this training and require both practitioner awareness of a switch and new training to effectively use any new device.

It is important to recognize that use of the SCS Microinjector in the suprachoroidal space is a specialized procedure that must be performed in accordance with the instructions detailed in the Xipere labeling. A healthcare practitioner must take particular care to perform the injection correctly, as the suprachoroidal space typically is collapsed prior to the injection of fluid, which means that visualization of the scleral-choroidal plane is not possible.¹⁰⁴ Rather, practitioners must rely on tactile cues to indicate when the sclera has been penetrated.¹⁰⁵ To that end, proper injection depends on syringe alignment perpendicular to the sclera, maintenance of the compression of the conjunctiva with the needle hub, and slow injection over 5-10 seconds. Users must also be aware of potential reflux from the injection site, minimization of which typically requires maintaining needle positioning for approximately thirty seconds to one minute throughout the entire injection procedure—in contrast with standard intravitreal injections that are typically completed within a few seconds.¹⁰⁶ User technique therefore is critically important but also highly dependent on user experience.¹⁰⁷

The controlled drug delivery and minimization of reflux that are reiterated and emphasized in training provided by Bausch+Lomb are critical to the success of the procedure. Indeed, Bausch+Lomb offers extensive training to health care professionals, which has been widely utilized. Practitioners receive a kit with a practice microinjector with the needle assemblies, synthetic eye for injection practice, and step-by-step instructions to prepare the vial and syringe and inject the formulation into the suprachoroidal space using the synthetic eye for practice injection. That training also educates practitioners on the appropriate microneedle based on patient characteristics and how to understand the “feel” of the resistance to recognize when to stop the injection attempt and to change needle. More technically, during training, physician-investigators are taught how resistance in the device corresponds to the

¹⁰⁴ Chiang (2018), *supra* n.55, at § 2.3.

¹⁰⁵ *Id.*

¹⁰⁶ *Id.*

¹⁰⁷ *Id.*

needle tip location and can be used to guide the injection.¹⁰⁸ Though the training itself is not mandatory, that practitioners take advantage of it is indicative of the care and precision necessary to successfully use the SCS Microinjector. Different training—and different instructions and labeling—inherently would be needed with a different injector.

Even though the injector is intended to be used only by a healthcare professional, that healthcare professional will need to know of, and be alert to, such differences or risks of user error would increase dramatically. Indeed, changes to the product could be significant enough that health care providers would need to “unlearn” Bausch+Lomb’s training to learn to use another product. Such a circumstance would raise serious concerns of confusion for practitioners automatically switched from Xipere to the generic. Even if training is not mandatory to use the SCS Microinjector, training *would be* necessary to address and bring awareness to any differences; without such additional training, a high likelihood of confusion arises.

Bausch+Lomb developed its training and related educational materials because most medical professionals are trained to inject into the intravitreal space; to use the SCS Microinjector, they must first be *untrained* to inject into the intravitreal space and *retrained* to inject into the suprachoroidal space. As noted, the procedures are complex and differ significantly from intravitreal injections and devices used for intravitreal injections. Changing the injector *again* to a different microinjector would require even more untraining and retraining for health care professionals. But FDA can only approve a generic combination product where the generic can be substituted for the RLD without additional training.¹⁰⁹

Where a change to the device component requires additional training, FDA will not approve that change in an ANDA.¹¹⁰ FDA has made clear that its review process for ANDAs for combination products “considers whether any difference in materials, design, or operating principles introduces a new risk[, including] consideration of both risks intrinsic to the new product *and risks associated with switching from one product to the other without additional . . . training.*”¹¹¹ Those

¹⁰⁸ Wan (2020), *supra* n.101, at 6.

¹⁰⁹ Combination Product Guidance, at 4 n.12 (“FDA does not necessarily expect for approval that a generic combination product can be used according to the RLD labeling per se, but rather it is critical that the generic combination product can be substituted for the RLD without additional physician intervention and/or retraining prior to use.”).

¹¹⁰ See *id.* at 5 (“In general, FDA expects that end-users of generic combination products, including but not limited to lay-persons . . . can use the generic combination product when it is substituted for the RLD . . . without additional training prior to use of the generic combination product.”).

¹¹¹ King Petition, *supra* n.26, at 6 (emphasis added).

risks are unavoidable should a follow-on use a different injector. To avoid these risks, the PSG should recommend use of the same injector as Xipere or require *in vivo* trials with the final to-be-marketed device and in-use studies with that injector showing that that the products can be used interchangeably.

Given these risks, FDA often requires testing of other combination drug-device products using *in vivo* methods to demonstrate that the RLD and generics can be used interchangeably. In the PSG for intra-articular triamcinolone acetonide suspension, for example, FDA requires an *in vivo* bioequivalence study with pharmacokinetic endpoints using the drug product. FDA takes the same approach—recommending *in vivo* studies using the device components in other PSGs for combination drug-device products.¹¹²

In this instance, given that Bausch+Lomb’s extensive training and education campaign applies specifically—and only—to the Xipere SCS Microinjector, the introduction of a different injector would inherently require healthcare practitioners to study and understand new injection procedures. If the new injector were to be a component of an automatically-substituted generic for Xipere and no such training and instruction provided, confusion would abound. Indeed, two different injectors for ostensibly the same product invites medical error, which is especially alarming in the case of an injection into the eye. That new training would be warranted to mitigate such risks indicates that a generic with a different injector should not be automatically substitutable for Xipere without additional data. The PSG therefore should recommend either use of the same injector as Xipere or studies to demonstrate both that the injector is safe and effective and that a switch in injectors would not raise additional risks.¹¹³

3. *In vivo* studies are necessary for any new injector.

Because no other type of injector is known to reliably, safely, and effectively access the suprachoroidal space in a clinical setting, the most prudent approach for

¹¹² FDA, PSG, Triamcinolone Acetonide Intra-Articular Suspension, NDA 208845 (Nov. 17, 2022). FDA requires PK bioequivalence and comparative clinical pharmacodynamic studies for Epinephrine aerosol metered inhaler, both using the test product devices. FDA, PSG, Epinephrine Aerosol, metered; inhalation, NDA 205920 (Nov. 18, 2020). Other examples abound.

¹¹³ King Petition, *supra* n.26, at 6 (“The Agency’s review process for ANDAs for combination products considers whether any difference in materials, design, or operating principles introduces a new risk,” including “risks associated with switching from one product to the other . . .”); Combination Product Guidance, at 4 n.12 (“FDA does not necessarily expect for approval that a generic combination product can be used according to the RLD labeling per se, but rather it is critical that the generic combination product can be substituted for the RLD without additional physician intervention and/or retraining prior to use.”).

FDA to adopt is to require use of the same injector by potential generic products referencing Xipere. As noted, any differences in injectors would change the risk profile such that safety and efficacy could not be extrapolated from the RLD. But Bausch+Lomb recognizes that use of the same injector may not be feasible. In such a case, Bausch+Lomb believes that FDA's PSG for Xipere should recommend *in vivo* studies using the new injector and switching studies.

While *in vitro* studies may be sufficient for triamcinolone acetonide on its own, findings from *in vitro* injections into the suprachoroidal space do not present an accurate depiction of how the product would work in live humans. Neither animal testing nor cadaver testing can replicate the injection process in live human eyes.¹¹⁴ Plainly, animal eyes are not the same as human eyes. While some animal eyes may be similar, they often have different anatomical barriers than humans; rabbit eyes, for example, which are typically used as stand-ins for human eyes, can differ with respect to circumferential particle spread, which is a critical aspect of delivery to the suprachoroidal space.¹¹⁵ The scleral thickness is also significantly different between human and rabbit eyes.

Even if such testing were done on a human cadaver instead of an animal, results also would not be representative, as the human eye changes dramatically after death due to a change in metabolism, which in turn impacts the opening of the suprachoroidal space.¹¹⁶ Further, the choroid and retina delaminate from the sclera at death, creating artificial space, and intraocular pressure decreases drastically after death, all of which distort findings.¹¹⁷ Natural pressure gradient, the driving force of uveoscleral outflow, is also absent in cadaveric eyes.¹¹⁸ Consequently, studies using animal eyes or cadaver eyes are inadequate to show *in vivo* absorption characteristics and do not provide an accurate representation of how the product would perform in live humans. Absent the same injector, *in vivo* testing of an ANDA referencing Xipere should be recommended in the PSG to adequately reflect the operation of the triamcinolone acetonide in live human eyes.

Admittedly, animal and cadaver eyes have been used to assess intravitreal triamcinolone acetonide products, but that is so because the intravitreal injections do

¹¹⁴ Yasemin Balci, et al., The Importance of Measuring Intraocular Pressure Using a Tonometer in Order to Estimate the Postmortem Interval, 31 Am. J. Forensic Med. Pathol. 151 (2010) (Exhibit 11); Bryce Chiang et al., Distribution of Particles, Small Molecules and Polymeric Formulation Excipients in the Suprachoroidal Space after Microneedle Injection, 153 Exp. Eye Res. 101, § 4.4 (2016) (Exhibit 12).

¹¹⁵ *Id.*

¹¹⁶ Miriam Kita & Michael Marmor, Effects on Retinal Adhesive Force in Vivo of Metabolically Active Agents in the Subretinal Space, 33 Investig. Ophthalmol. Vis. Sci. 1883, 1885 (1992) (Exhibit 13).

¹¹⁷ *Id.*

¹¹⁸ Emi, *supra* n.55, at 238.

not require a specialized delivery mechanism for safe and elective deposit of medicament. Indeed, notwithstanding their similarities, there are totally different questions that apply to intravitreal generic drugs and suprachoroidal drugs; the intravitreal PSG is intended to address whether that location would have the desired treatment effect while the suprachoroidal PSG must look at whether the location has the desired treatment effect *and* whether the delivery device can safely and accurately deposit the medicament into that location (i.e., the suprachoroidal space). As noted and to that point, it was not the triamcinolone acetonide that was investigated for safety and efficacy in the approval of Xipere but the location of the deposit of the medicament and the means of delivery; the same does not apply to intravitreal triamcinolone acetonide, which was reviewed only for effectiveness of the drug in a new indication and adequacy of a new preservative-free formulation, can be used with any off-the-shelf device for delivery, and is not approved as a combination product.¹¹⁹

In other products where the delivery device or device constituent is an integral part of the drug product, FDA has required similar *in vivo* studies. For intrauterine devices, for example, where the device itself is as critical as the copper active ingredient, FDA requires *in vivo* studies even if the proposed follow-on product is identical in active and inactive ingredients, in t-frame dimensions, and in physicochemical and mechanical properties, and has comparable *in vitro* cupric ion release rate to the RLD.¹²⁰ This is because of the complexity of demonstrating bioequivalence where the product is both the drug and delivery system. Xipere is a similar inextricably-linked drug and delivery system.

FDA also took a similar approach with extended-release triamcinolone acetonide for intra-articular delivery. Even with a formulation that is Q1/Q2, acceptable physicochemical characterization of both the test and reference products, and *in vitro* drug release, FDA required *in vivo* bioequivalence studies with PK endpoints.¹²¹ Thus, a matching formulation is not enough: How it is delivered to the actual treatment area—here, the knee—is important to bioequivalence. The same applies here where the placement of the suprachoroidal formulation by way of the specific drug delivery system significantly affects the function of the product. Bioequivalence of the formulation without consideration of the device misses the concerns that arise due to the tandem use of the drug and device relying on such a complicated route of administration.

Where, like here, a drug and device are so integrated that similarity of the individual components is not sufficient to ensure bioequivalence, FDA has not

¹¹⁹ NDA 22048, Clinical Review, at 8 (Oct. 24, 2007).

¹²⁰ FDA, PSG, Copper Intrauterine Devices, NDA 018680 (Nov. 2019).

¹²¹ FDA, PSG, Triamcinolone Acetonide Intra-articular suspension, NDA 208845 (Nov. 2022).

hesitated to require *in vivo* studies. FDA should require the same with respect to ANDAs referencing Xipere where the proposed injector differs from the SCS Microinjector.

4. At a Minimum, the Same Design, Operation, and Functionality as the SCS Microinjector is Necessary to Ensure the Same Performance as the RLD.

The draft PSG asks potential generic applicants to “examine” the device attributes but does not recommend the same characteristics, any comparability testing, or any *in vivo* testing. Though Bausch+Lomb believes that any generic drug referencing Xipere should be provided with the same injector, at a minimum, FDA should require the same critical features.

The device constituent in some drug and device products may be amenable to design or operating differences, but Xipere is not one of those products. As noted, changes to the SCS Microinjector integrated into Xipere will impact the performance of the product. After years of research, Clearside developed and manufactured multiple iterations of a delivery device specifically to inject triamcinolone acetonide into the complicated suprachoroidal space safely and effectively, and indeed all facets of the SCS Microinjector specifically are designed to do so.¹²² Through clinical and usability studies, Clearside identified features that are critical to such a drug delivery device and integrated them into the critical features of the SCS Microinjector. Ultimately, Clearside identified microneedle length and bevel, plunger force, and volume delivered as the critical features that must be met for safe and effective use.¹²³ Consequently, should FDA determine that a potential generic application need not use the same injector as Xipere, the draft PSG should be revised to, at a minimum, *require* any such ANDAs use a microinjector with the same critical features as the SCS Microinjector.

The microneedle itself may be the most important component of the SCS Microinjector. Research shows that only a hollow-bore needle with a length of 1 mm or less can be used to deliver medicament to the suprachoroidal space without piercing the choroidal vasculature or any underlying structures.¹²⁴ The length of the microneedle must be chosen with consideration of the scleral and conjunctival thickness at the pars plana. The needle must be physically unable to penetrate through the choroid and retina or it would perform an inadvertent intravitreal injection. Because this is a significant risk with use of a standard hypodermic needle and syringe,¹²⁵ the SCS Microinjector was designed as a proprietary manual piston

¹²² Kansara (2022), *supra* n.71, at 1046.

¹²³ NDA 211950, Intercenter Consult Memorandum, at 5 (Aug. 1, 2019).

¹²⁴ Chiang (2018), *supra* n.55, at § 2.3; Hartman (2018), *supra* n.92, at 148.

¹²⁵ Muya (2022), *supra* n.61, at 464-65; Chiang, *supra* n.114, at 4.

syringe to be used with one of two 30-gauge needles measuring either 900 µm or 1100 µm, which accommodate anatomic variation in human eyes such that the needles are long enough to pass through the sclera without penetrating through the choroid, retina or vitreous.¹²⁶ Additionally, the needle bevel is very specific in design—bevel angles, opening size, overall length, and tri-bevel design—to avoid the possibility of accidental subconjunctival or intravitreal injections. Thus, the needle length and bevel are so critical to the safe and effective delivery of triamcinolone acetonide suprachoroidal injection such that any differences could seriously impact its risk profile.

Further, the SCS Microinjector depends heavily on the plunger force used in delivery of the drug.¹²⁷ Ensuring that any follow-on device provides the same force is important because the hydrodynamic force of the injection opens the suprachoroidal space such that the fluid flows circumferentially around the eye between the sclera and choroid.¹²⁸ Additionally, during the injection procedure, access to the suprachoroidal space is confirmed by intraprocedural loss of resistance, at which point injectate flows into the suprachoroidal space circumferentially and peripherally;¹²⁹ reduction in force required to overcome syringe plunger resistance assists the physician in feeling the loss of resistance to ensure proper placement of the injection.¹³⁰ Lower injection forces translate to a clearer tactile perception of loss of resistance during the injection procedures, which signals to the clinician that the microneedle tip is in the suprachoroidal space; persistent resistance signals that a longer needle is necessary.¹³¹ For this reason, the SCS Microinjector includes features that ensure that the proper amount of force is used: When the needle tip is located within the sclera, injectors feel resistance from the plunger, preventing off-target drug delivery, and when the needle tip is advanced beyond the sclera into the suprachoroidal space, injectors feel a loss of resistance and the plunger will readily advance smoothly and easily to inject drug into the suprachoroidal space.¹³²

Thus, certain design elements of the SCS Microinjector are necessary to assist with positioning and injecting. This includes, for example, a unique handle design that allows only pushing forward—rather than pulling back—so that physicians can feel the injection to confirm the correct positioning of the injector in the eye. Other design features include functionality, injection volume, plunger aspiration force,

¹²⁶ Kansara (2022), *supra* n.71, at 1046; Wan (2020), *supra* n.101, at 6.

¹²⁷ Hartman (2018), *supra* n.92, at 148-50.

¹²⁸ Yoo Chun Kim et al., Formulation to target delivery to the ciliary body and choroid via the suprachoroidal space of the eye using microneedles, 95 Eur. J. Pharm. Biopharm. 398, 399 (2015).

¹²⁹ Chiang (2018), *supra* n.55, at § 2.3; Wan (2020), *supra* n.101, at 6.

¹³⁰ Muya (2022), *supra* n.61, at 465.

¹³¹ *Id.*

¹³² Wan (2020), *supra* n.101, at 6.

needle length, and plunger depression force tests, all of which are critical measurements developed specifically for the device constituent of Xipere.¹³³

It is clear that both the device and its specific features are important to the safe and effective use of Xipere, particularly, as discussed below, in the use of triamcinolone acetonide in a combination product. Given the importance of these features, FDA should require all ANDAs referencing Xipere to include an injector that is the same, in all the meaningful ways discussed, as the SCS Microinjector or require *in vivo* testing using the proposed formulation of triamcinolone acetonide.

D. A Q1/Q2 Formulation is Necessary but Not Sufficient to Demonstrate Bioequivalence to Xipere.

Bausch+Lomb appreciates that the draft PSG recommends that any ANDA referencing Xipere have the “same inactive ingredients” in “the same concentration”—or Q1/Q2 the same—as the RLD other than exception excipients, as well as the recommendation for comparative physicochemical characterization of the RLD and proposed generic. Bausch+Lomb is nevertheless concerned that the draft PSG omits certain critical physicochemical characteristics that facilitate the safe and effective use of Xipere, such as syringeability and glide force.¹³⁴ These characteristics—and others, like milling, and order of mixing—can all affect bioequivalence even across Q1/Q2 products, as well as affect the functionality of the SCS Microinjector.¹³⁵

Without mandating that a follow-own formulation have characteristics modulated specifically for optimal drug delivery, it is possible that even a Q1/Q2 product could have different clinical effects.¹³⁶ In particular, for ophthalmic products in nonsolution dosage forms, matching ingredient profiles may not result in

¹³³ The need for specific microneedle lengths and bevels, as well as the need for features that ensure the same force profile as the SCS Microinjector, render most off-the-shelf injector inadequate. While it is possible that an off-the-shelf injector could have the correct needle bevels, it is unlikely that any would have the appropriate size needles. Further, most off-the-shelf needle hub shapes, molding, and adhesive could cause injury. Standard off-the shelf syringes also have much shorter syringe plunger travel distance for 0.1 mL dose volume, risking the critical procedure step of slow injection, while also decreasing the precision of the volume and dose delivered.

¹³⁴ See FDA, PSG, Triamcinolone Acetonide suprachoroidal injection, NDA 211950 (Feb. 16, 2023).

¹³⁵ Ahmad A. Aref, Generic drugs for the treatment of ocular conditions: changing the treatment landscape, 7 Expert Rev. Clin. Pharmacol. 551, 551-52 (2014) (Exhibit 14); Wiley A. Chambers, Ophthalmic Generics – Are They Really the Same?, 119 J. Ophthal. 1095, 1096 (2012) (Exhibit 15).

¹³⁶ *Id.*, at 1096.

consistently comparable drug compositions and clinical effects.¹³⁷ 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.¹³⁸ Consequently, it is important not only to ensure that the active and inactive ingredients are the same but also that they are formulated the same way such that product characteristics, such as molecular weight, glide force, and syringeability, are comparable to—if not the same as—the RLD.

The most important feature of the Xipere formulation is the syringeability. Syringeability refers to the performance of a formulation during injection.¹³⁹ Factors such as ease of withdrawal, clogging and foaming tendencies, accuracy of dose, and evenness of flow can all go to injection success.¹⁴⁰ Physicochemical factors of both the device—such as the needle geometry and surface finish of the syringe—and formulation factors—such as viscosity and particle size—play a significant role in syringeability.¹⁴¹ For example, if particles are too big—like the formulations used in Kenalog or Triesence—or if they stick to each other, it directly affects injection success, as such particles would get stuck while moving through the SCS Microinjector.¹⁴² If the particles are milled too finely, the drug will not deposit properly in the SCS; instead, it would be absorbed into the vasculatures and carried away in circulation. Thus, the characteristics related to syringeability are critical to the risk and benefit profile of the product.

However, measuring only a few factors that impact syringeability, namely particle size distribution and viscosity, is not sufficient. This is because syringeability, in the context of Xipere, includes much more. Specifically, syringeability includes whether and how particles stick to each other for reasons other than particle size. And with the formulation of triamcinolone acetonide used in Xipere, there is a high probability that particles *will* stick to each other thereby impacting the functionality of the microinjector. To address these syringeability issues, Xipere relies on a complex sonication process that breaks up the agglomeration of particles during manufacturing and rigorous testing has been performed that validate its effectiveness. Each particle is also coated with a proprietary substance to preclude self-adhesion. Sonication therefore is critical to the successful injection of Xipere, which is precisely why FDA required Clearside to develop testing methods to show the statistical differences between each point of sonication. The sonication process used in Xipere may not need to be replicated

¹³⁷ Aref, *supra* n.135, at 551.

¹³⁸ Chambers, *supra* n.135, at 1096.

¹³⁹ Stephanie H. Choi et al., Generic drug device combination products: Regulatory and scientific considerations, 544 Int. J. Pharm. 443, 449 (2018) (Exhibit 16).

¹⁴⁰ *Id.*

¹⁴¹ *Id.*

¹⁴² *Id.*

exactly, but it is important that any ANDA referencing Xipere address the potential adhesion issue and demonstrate that the formulation selected will not clog the syringe or microneedle.

Glide force is also “an integral attribute” for successful use of the SCS microinjector.¹⁴³ Glide forces impact tactile perception of loss of resistance during the SCS microinjection procedure. Lower and less variable glide force provide clearer tactile perception, allowing practitioners to know whether they have successfully entered the SCS.¹⁴⁴ But glide forces vary even between drug products of the same active ingredient; intravitreal triamcinolone acetonide, for example, has a statistically higher and more variable glide force than that of the triamcinolone acetonide used in the Xipere.¹⁴⁵ This is because particle size distribution, surfactants, viscosity enhancing agents, and other factors of excipients can significantly impact a drug product’s performance using an SCS microinjector, including consistency in drug product performance.¹⁴⁶ Thus, because of the need to formulate the triamcinolone acetonide specifically for use in the SCS Microinjector, the triamcinolone acetonide formulation used in Xipere is itself different from other triamcinolone acetonide products.

Even though it is the device constituent that renders Xipere so novel, an ANDA formulation must have the same physicochemical properties as Xipere to ensure functionality of the injector. Matching active and inactive ingredients is not sufficient when factors like syringeability and glide force can impact compatibility of the formulation with the injector. Consequently, FDA should require that any ANDA referencing Xipere include additional comparisons of physicochemical characteristics that analyze both sameness in formulation as well as sameness in function. Furthermore, injection volume, plunger aspiration force and plunger depression force tests are especially important to be evaluated *in tandem with the proposed formulation* as a combination product, where the specific triamcinolone acetonide formulation and the SCS Microinjector are purposefully designed to work together.¹⁴⁷

E. Conclusion

Xipere was developed as a combination product such that the device component is as important to the safety and efficacy of the product as the drug component. For that reason, it is critical that any proposed ANDA referencing Xipere have the same safety and efficacy profile as that of the SCS Microinjector included in Xipere. Given the complexity of drug delivery to the suprachoroidal space, the only

¹⁴³ Muya (2022), *supra* n.61, at 465.

¹⁴⁴ *Id.*

¹⁴⁵ *Id.*

¹⁴⁶ *Id.*

¹⁴⁷ See NDA 211950, Intercenter Consult Memorandum, at 5 (Aug. 1, 2019).

way to ensure the same safety and efficacy profile is to require that any such ANDA utilize the same injector as Xipere. Absent the same injector, the safety and efficacy of a generic version of Xipere should be demonstrated through *in vivo* studies and switching studies showing that the product can be used interchangeably with Xipere. Without such studies, FDA cannot ensure that any differences “do not significantly alter product performance or operating principles” and that the product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.¹⁴⁸ Any differences would further require additional training prior to the use of the generic product.

To that end, Bausch+Lomb requests that FDA revise its February 2023 draft PSG to require that any ANDA referencing Xipere use the same device or provide *in vivo* studies with clinical endpoints and in-use switching studies, demonstrating the safety and effectiveness of the new injector. Further, Bausch+Lomb requests that the PSG include additional physicochemical characteristic comparisons, such as syringeability and glide force, to ensure “sameness” of the proposed generic product and Xipere.

III. ENVIRONMENTAL IMPACT

The undersigned claims a categorical exclusion from the requirements for an Environmental Assessment under 21 C.F.R. § 25.31(a) because the grant of this Citizen Petition would not have an effect on the environment.

IV. ECONOMIC IMPACT

An economic impact statement will be submitted at the request of the Commissioner.

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: February 16, 2023. If I received or expect to receive

¹⁴⁸ See King Petition, *supra* n.26, at 6.

payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following person or organizations: Bausch+Lomb. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.¹⁴⁹



Kris Tucker
Senior VP, Global Regulatory Affairs
Bausch+Lomb

¹⁴⁹ This Petition has been withdrawn and resubmitted at the request of FDA due to the omission of a certification under section 505(q) of the FDC Act. Petitioner is unaware of any follow-on applications referencing Xipere (triamcinolone acetonide) and has not received any Paragraph IV Notice but has nonetheless resubmitted with the requested certification.