UNITED STATES INTERNATIONAL TRADE COMMISSION
WASHINGTON, D.C.

In the Matter of CERTAIN PRE-FILLED SYRINGES FOR INTRAVITREAL INJECTION AND COMPONENTS THEREOF	Investigation No. 337-TA-____ Docket No. 3460

STATEMENT ON THE PUBLIC INTEREST BY PROPOSED RESPONDENT REGENERON PHARMACEUTICALS, INC.

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Proposed Respondent Regeneron Pharmaceuticals, Inc. respectfully submits this public interest statement in response to a complaint entitled *Certain Pre-filled Syringes for Intravitreal Injection and Components Thereof*, DN 3460, filed on June 19, 2020. *See* 85 Fed. Reg. 38158. As discussed below, the relief sought in the Complaint would be severely detrimental to the public health because it would disrupt the treatment regimens for patients suffering from serious eye diseases, eliminate physician choice to ensure the best therapies for their patients, and force patients benefiting from the accused product to switch to other drugs that are less effective and in some cases even unsafe.

I. HOW THE ACCUSED PRODUCTS ARE USED IN THE UNITED STATES

Complainants seek to bar the importation of Regeneron's EYLEA® (aflibercept) pre-filled syringe ("PFS") and components thereof. EYLEA is an innovative biologic drug for the treatment of a variety of severe eye diseases involving overproduction of a naturally occurring protein called vascular endothelial growth factor ("VEGF"). Millions of patients suffer from VEGF-related eye diseases that can cause vision loss and blindness, including (among others) wet age-related macular degeneration ("wet AMD"), diabetic retinopathy ("DR"), diabetic macular edema ("DME"), and macular edema following retinal vein occlusion ("MEfRVO"). EYLEA is FDA-approved to treat all of these diseases.

EYLEA is a novel and groundbreaking drug developed by Regeneron that blocks or inhibits the overproduction of VEGF proteins, reducing abnormal growth and leakage in the eye, which helps to stabilize vision loss. In some cases, EYLEA can even reverse vision loss and restore sight. After years of research and development, EYLEA first received FDA approval in vial form in November 2011. FDA approved EYLEA in PFS form on August 13, 2019. Regeneron started selling EYLEA PFS on December 9, 2019, and commenced a full-scale commercial launch in February 2020. After only months on the market, physicians and patients rapidly switched from EYLEA vial to EYLEA PFS, with nearly 80% of EYLEA sales converting to PFS form. Nearly all EYLEA sales will likely convert to PFS within the year.

II. THE REQUESTED RELIEF POSES SUBSTANTIAL PUBLIC HEALTH CONCERNS

A. Patients Should Not Be Forced to Switch to EYLEA in Vial Form

Complainants contend that excluding EYLEA PFS would have no adverse impact on the public

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health because physicians can simply switch from administering EYLEA PFS to EYLEA with a vial and syringe – this is simply untrue for several reasons. First, as shown in Fig. A below, EYLEA in vial form comes with many more components than PFS, including the vialed biologic, two separate needles, a plastic syringe, and not to mention all the packaging.

Fig. A: EYLEA Vial

Fig. B. EYLEA PFS

Thus a physician must utilize two needles, along with the vialed biologic, to undergo the sterile process of withdrawing the anti-VEGF from the vial (using a filter needle) before injecting it into the patient's eye (using an injection needle). By contrast, the PFS (shown in Fig. B above) is a single, integrated safety system injection product and comes ready-to-use as soon as the physician attaches a separate needle for injection. Thus, administering EYLEA in vial form, by definition, has more touch points, is more time-consuming, increases the number of steps and thereby the possibility of foreign particles being introduced into the eye during administration. It is no surprise that physicians as well as patients prefer the PFS over the vial given its ease of use and efficiency.

Moreover, switching the many millions of patients now relying on their regular injections of EYLEA PFS to injection with a separate needle from a vial would be impractical from a supply standpoint. Regeneron and its manufacturing partners have already transitioned their manufacturing and supply operations from EYLEA in the vial to EYLEA in PFS. To transition the manufacturing process back to the EYLEA vial would take several years to accomplish, assuming the manufacturing lines are

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even available. If those manufacturing lines are not available and Regeneron were forced to develop new manufacturing partners or facilities, the process of procuring equipment, developing and validating the manufacturing process, and obtaining regulatory approval would take even longer. As such, Regeneron cannot predict when or how many EYLEA vials would be available for patients currently relying on EYLEA PFS. EYLEA in vial form is thus not an acceptable substitute for EYLEA PFS.

B. LUCENTIS Is Less Effective and Less Convenient than EYLEA PFS

There is no acceptable substitute for EYLEA PFS. Complainants contend that their own anti-VEGF product LUCENTIS is an acceptable substitute. But Lucentis requires more frequent injections than EYLEA at a time when in-patient trips to medical doctors are difficult with the COVID-19 pandemic. Unlike LUCENTIS, EYLEA is recommended for intravitreal injection once a month for the first three months, but then can be injected every two months to treat wet AMD, DR, and DME. Regeneron clinical studies showed that EYLEA administered every two months was clinically equivalent to LUCENTIS dosed monthly. Indeed, EYLEA involves "less frequent injections and monitoring. This may reduce the need for costly and time-consuming monthly visits for patients and caregivers."[1] Moreover, because of its unique design, EYLEA is likely to bind the VEGF target more tightly than LUCENTIS (which has only one VEGF binding domain), resulting in a stronger inhibition of VEGF in the patients' eyes. EYLEA has also been found to be more effective at improving vision for patients with DME.[2] EYLEA is therefore regarded by many as superior to LUCENTIS.

LUCENTIS is not an acceptable substitute for EYLEA PFS for the additional reason that physicians are naturally reluctant to switch a patient from one anti-VEGF to another when the patient is responding well to a particular treatment. Moreover, insurance approval for EYLEA is not transferable to LUCENTIS, so patients would experience additional delays and inconvenience if they were forced to

[1] Press Release, Regeneron, "Regeneron Announces FDA Approval of EYLEA™ (aflibercept) Injection for the Treatment of Wet Age-Related Macular Degeneration," (Nov. 18, 2011), https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-fda-approval-eylea153-aflibercept-injection.

[2] *See* Diabetic Retinopathy Clinical Research Network, *Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema*, N. Engl. J. Med. 372(13) (Mar. 26, 2015).

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switch treatment.

III. OTHER FDA-APPROVED DRUGS CANNOT REPLACE EYLEA PFS

Aside from EYLEA in the vial and LUCENTIS, Complainants identify no other FDA-approved anti-VEGF drugs for ophthalmic diseases at issue. Indeed, the only other such product that is prescribed with any meaningful regularity is Complainants' own anti-VEGF product BEOVU, and only for wet AMD. But within months of BEOVU's launch in 2019, patients started suffering from a range of severe safety issues. Physicians immediately began reporting serious adverse reactions experienced by BEOVU patients, including higher rates of intraocular inflammation, incidences of retinal artery occlusion, and occlusive retinal vasculitis. These are urgent medical conditions that can result in permanent blindness. In fact, Novartis's own worldwide brand medical director urged Novartis to disclose its clinical study data regarding the adverse health effects of BEOVU. Instead, Novartis terminated her employment, and a wrongful termination suit is currently pending in the District of New Jersey. *See Butuner v. Novartis Pharm. Corp.*, Case No. 19-cv-06590-ES-MAH (D.N.J.).

Moreover, the American Society of Retinal Specialists has released *five* safety bulletins this year, advising physicians that it had received reports of severe inflammation in patients injected with BEOVU.[3] In response, Novartis conducted an external safety review of BEOVU, examining post-marketing events in patients compared to its clinical trial results. Novartis ultimately sought FDA approval of an updated label for BEOVU, highlighting its safety risks. FDA forced Novartis to acknowledge that BEOVU may cause adverse events in patients of "retinal vasculitis and/or retinal vascular occlusion ***that may result in severe vision loss***."[4] BEOVU is thus not an acceptable replacement for EYLEA PFS, which has experienced no such safety issues.

IV. NO SUPPLIER HAS THE CAPACITY TO REPLACE THE ACCUSED PRODUCTS

For the reasons stated above, no supplier has the capacity to provide a safe, acceptable

[3] *See* ASRS, Clinical Updates, https://www.asrs.org/clinical/clinical-updates.
[4] Press Release, Novartis, "Novartis Completes Safety Review and Initiates Update to the Beovu® Prescribing Information Worldwide (Apr. 8, 2020), https://www.novartis.com/news/novartis-completes-safety-review-and-initiates-update-beovu-prescribing-information-worldwide (emphasis added).

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