March 5, 2023

C. Randall Harrell MD, Chairman & CEO
Regenerative Processing Plant LLC
34176 US Hwy 19 N
Palm Harbor, FL 34684

OPEN LETTER TO REGENERATIVE PROCESSING PLANT LLC

Is the Regener-Eyes bottle safe?

Dear Dr. Harrell:

The Dry Eye Foundation is a 501(c)(3) nonprofit organization serving the ocular surface disease and ocular surface pain patient communities(1).

As part of our education mission, we are actively engaged in raising awareness about safety trends of concern in the over-the-counter eye drop space (2) (3).

In January 2022, a colleague and I (4) visited the Regener-Eyes LLC booth at the Global Specialty Lens Symposium in Las Vegas. We were offered samples of Regener-Eyes Professional Strength and Regener-Eyes Lite, sent to us later by mail. I later purchased more online. I observed that both types of Regener-Eyes eye drops were packaged in simple multi-dose bottles with no preservative-free dropper to protect against bacterial contamination after opening (Image 1). This prompted strong concern and considerable research.

In April 2022, Dry Eye Foundation began communicating with the Office of Jurisdiction at the Food and Drug Administration's Center for Biologics Evaluation and Research about Regener-Eyes; we have subsequently communicated with other CBER offices as well as offices at the Center for Drug Evaluation and Research. Our stated concerns included but were not limited to: (a) absence of an ingredient list; (b) absence of a backwash prevention device in the bottle, which we believed to be unprecedented for commercialized preservative-free multi-dose OTC substances intended for use on the ocular surface; (c) absence of a stated indication for use; and (d) absence of evidence that clinical trials had been completed to establish the safety of the products.

In May 2022, Dry Eye Foundation launched a public education campaign about biologic eye drop safety. This campaign began with two presentations by our medical advisor (5). The first (6) addresses safety concerns associated with potential bacterial contamination of preservative-free eye drops in multi-dose bottles. The second (7) addresses five misconceptions about biologic eye drops that were common at that time, relating to FDA approval status, clinical trials, prescription drug status, OTC drug status, and evidence of sterility during use.

In June 2022, Dry Eye Foundation publicly identified Regener-Eyes brand products as biologic eye drops of concern (8) and in ensuing months our medical advisor produced several additional educational presentations related to Regener-Eyes.

In August and September 2022, Regener-Eyes:

- progressively modified its branding and advertising, removing all references to biologic substances, and even changing the company slogan (Image 2);
- updated its OTC product listings, replacing "d-MAPPS", an ingredient with identifiable biologic originss, with "Tonicity Solution", an unidentified ingredient with no UNII (9) (10);
- began describing Regener-Eyes as OTC (11); and
- began stating to consumers that Regener-Eyes "is FDA approved" or - if the caller persisted in their questioning - that Regener-Eyes "has an approved indication for dry eye" (12).

In September 2022, my colleague (4) and I again attended a trade show where Regener-Eyes was exhibiting (13). There, we witnessed your company marketing Regener-Eyes to physicians as a biologic through the distribution (Image 3) of an EyeWorld White Paper (14) which describes Regener-Eyes as an "engineered biological product", "derived from human placental-based biomaterials" and "immunomodulatory". At the same time, your company was also distributing a Regener-Eyes brochure stating that Regener-Eyes is "not immunosuppressive" (Image 4).

On September 22, 2022, Regener-Eyes sent a Cease and Desist letter to Dry Eye Foundation's medical advisor (5), who had communicated with members of Regener-Eyes' Clinical Advisory Board about Dry Eye Foundation's safety concerns.

On September 29, 2022, Dry Eye Foundation sent Regener-Eyes an Open Letter (15) requesting to know the ingredients of Regener-Eyes, on the basis that the Code of Federal Regulations requires manufacturers to provide this information on the product packaging (16).

On October 3, 2022 Regener-Eyes sent a Final Cease and Desist Demand letter to Dry Eye Foundation's medical advisor. You demanded, among others, that she remove 24 educational presentations. The first in your list for removal was a presentation about potential bacterial contamination of preservative-free eye drops in multi-dose bottles (6).

On October 5, 2022, Regener-Eyes sent Dry Eye Foundation a "Cease and Desist Demand" letter wherein you characterized our request for ingredient information as an attempt on our part to intrude into your "trade secrets".

On October 5, 2022, the Food and Drug Administration sent Regener-Eyes an Untitled Letter (17).

On February 1, 2023, the Center for Disease Control and Prevention issued an emergency HAN alert (18) about Ezricare Artificial Tears, which has been linked to a multi-state outbreak of multi-drug resistant Pseudomonas aeruginosa infections, with outcomes including loss of vision and one death. Ezricare Artificial Tears and Delsam Pharma Artificial Tears have since been recalled (19). ***Both CDC and FDA drew attention to the fact that these products, though preservative-free, were packaged in [simple] multi-dose bottles (20) (21).***

On February 21, 2023, I purchased Regener-Eyes Lite online. Upon receiving the product, I observed that the bottle appears unchanged from 2022, that is, it is a simple multi-dose bottle with no preservative-free dropper. Additionally, the most recently purchased product has no lot number or expiration date on the bottle (Image 5).

We therefore ask in this Open Letter:

1. Is Regener-Eyes preservative-free, as advertised?

The ingredient list on DailyMed states in the on-screen version that Regener-Eyes contains glycerin, "Tonicity Solution", and water (22) but states in the printable or downloadable version that it contains only glycerin and water (Image 6). Tonicity Solution has no Unique Ingredient Identifier (UNII). We do not know how it was possible for this ingredient to be listed in your FDA OTC registration without a UNII. In short, we do not know what Tonicity Solution is or whether Regener-Eyes contains it.

We have been informed by both a patient (23) and a Key Opinion Leader optometrist (24) that a Regener-Eyes sales person advised them - in explanation of the bottle type - that Regener-Eyes is "naturally antimicrobial". If this is a position your company supports, please explain what it means and what basis you have for believing that your bottle satisfies 21 CFR 200.50(b).

2. If Regener-Eyes is preservative-free, how is bacterial contamination prevented during use, given that it is packaged in a simple multi-dose bottle?

Your 3mL bottle contains approximately 60 drops.

No directions are provided with respect to how long the bottle may be used after opening (Image 5).

The dropper on your bottle audibly sucks air and visibly sucks liquid back into the bottle after dispensing a drop (25).

What evidence do you have that this packaging protects the contents from bacterial contamination in satisfaction of 21 CFR 200.50(b)?

We patients have a right to know what is in our eye drops and whether they are safe.

Recent tragic outcomes of the Pseudomonas aeruginosa infections related to EzriCare Artificial Tears have suggested how much is at stake when eye drop manufacturers disregard rules for manufacturing and packaging.

The Dry Eye Foundation eagerly anticipates a definitive resolution to the questions of what is in Regener-Eyes, whether it is preservative-free, and whether it is subject to bacterial contamination after opening.

Sincerely,

Rebecca Petris
President

NOTES

(1) http://www.dryeyefoundation.org
(2) http://www.eyedropsafety.org
(3) http://www.biologiceyedrops.org
(4) Aidan Moore, Board of Directors, Dry Eye Foundation, co-founder and member since 2018
(5) Sandra Brown MD, Board of Directors, Dry Eye Foundation, member since 2020
(6) https://www.biologiceyedrops.org/non-preserved-eye-drop-safety
(7) https://www.biologiceyedrops.org/watch/biologic-eye-drops-clearing-up-misconceptions
(8) https://youtu.be/Ji84Tje7mGg
(9) https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=643289
(10) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e7796d0d-13d7-73c3-e053-2995a90a8bde
(11) https://www.regenereyes.com/our-products/
(12) Personal communications with Regener-Eyes LLC, September 12-14, 2022
(13) https://west.visionexpo.com/en-us/expo-hall/exhibitor-list/exhibitor-details.org-9f0b5512-a9fe-4ed9-9af2-63fb71ebf365.html#/
(14) https://supplements.eyeworld.org/eyeworld-supplements/regener-eyes-white-paper-final-spread-foruberflip
(15) https://www.biologiceyedrops.org/watch/open-letter-to-regenerative-processing-plant-llc
(16) https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-201
(17) https://www.fda.gov/media/162219/download
(18) https://emergency.cdc.gov/han/2023/han00485.asp?ACSTrackingID=USCDC_511-DM98842&ACSTrackingLabel=HAN%20485%20-%20General%20Public&deliveryName=USCDC_511-DM98842
(19) https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/global-pharma-healthcare-issues-voluntary-nationwide-recall-artificial-tears-lubricant-eye-drops-due
(20) https://emergency.cdc.gov/han/2023/han00485.asp?ACSTrackingID=USCDC_511-DM98842&ACSTrackingLabel=HAN%20485%20-%20General%20Public&deliveryName=USCDC_511-DM98842
(21) https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-not-purchase-or-use-ezricare-artificial-tears-due-potential-contamination
(22) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e7796d0d-13d7-73c3-e053-2995a90a8bde
(23) Personal communication, December 2022
(24) Personal communication, September 2022
(25) https://youtu.be/onMQAYlmmLc

COPIES TO:

Food and Drug Administration

Center for Biologics Evaluation and Research
- Melissa Mendoza, JD - Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Compliance and Biologics Quality
- Robert Sausville, Director, Division of Case Management
- Maria Anderson, Supervisory Consumer Safety Officer, Biological Drug and Device Compliance Branch
- Monique Lester, Consumer Safety Officer, Biological Drug and Device Compliance Branch
- Jonathan Swoboda, Consumer Safety Officer, Biological Drug and Device Compliance Branch

Center for Drug Evaluation and Research
- Carolyn Becker, JD, Office of Unapproved Drugs and Labeling Compliance

Regener-Eyes LLC Clinical Advisory Board

Eric Donnenfeld MD
Marguerite McDonald MD
Sandra Cremers MD
Bennett Romanoff MD

Image 1: Regener-Eyes bottle, 2022

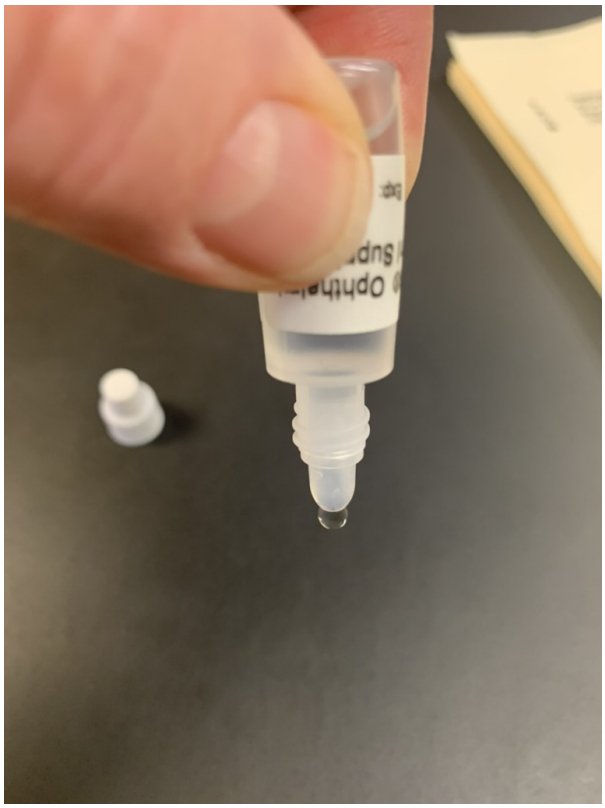
January 2022	April 2022
	

Image 2: Examples of Regener-Eyes marketing modifications

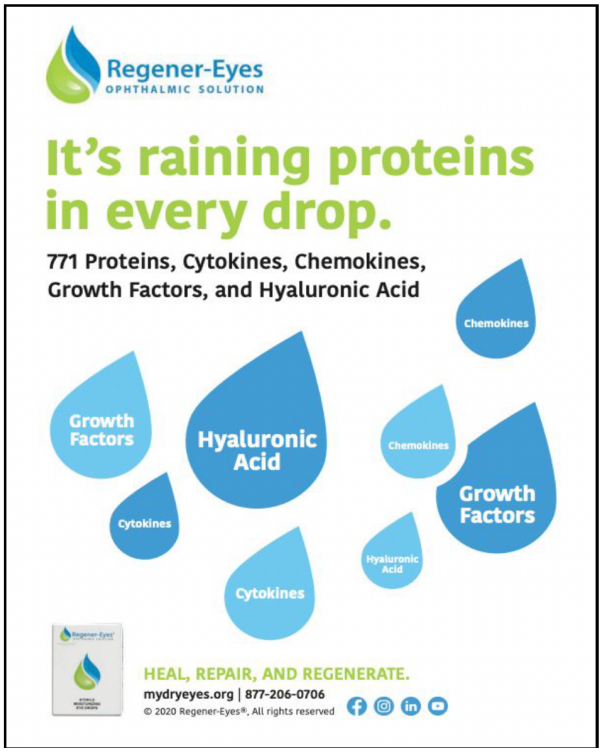
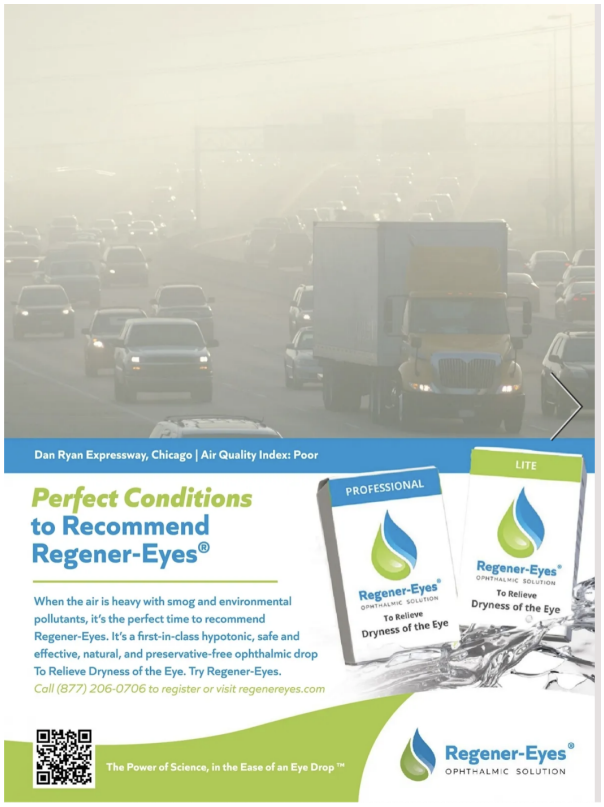
Before August 2022	**After August 2022**
Slogan: THE ***POWER*** OF A BIOLOGIC, IN THE ***EASE*** OF AN EYE DROP.	Slogan: THE ***POWER*** OF SCIENCE, IN THE ***EASE*** OF AN EYE DROP. ™
Full page ad, Review of Optometry March 2021 	Full page ad, Optometric Management October 2022 

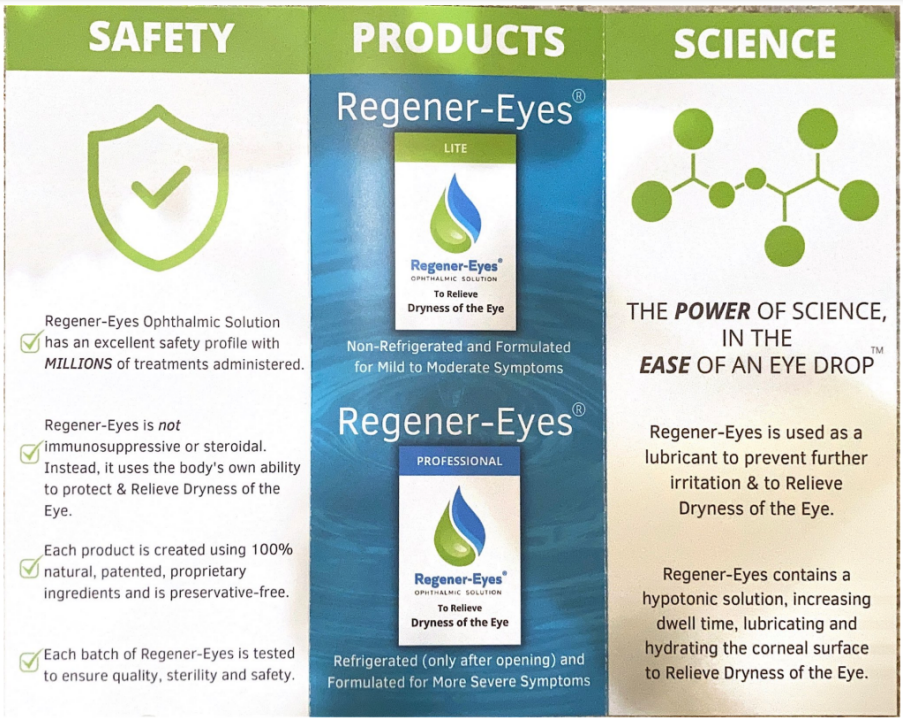
Image 3: Regener-Eyes booth, Vision Expo West, Las Vegas NV, September 2022

In foreground: Stack of Regener-Eyes brochures. This brochure (see Image 4) states that Regener-Eyes is "not immunosuppressive".

Behind brochures: Stack of reprints of an EyeWorld White Paper from June 2021 (see link). This paper describes Regener-eyes as "immunosuppressive" and an "engineered biological product"

Image 4: Regener-Eyes brochure, Vision Expo West, Las Vegas, September 2022

(Inside)



(Outside)

Image 5: Regener-Eyes, February 2023

(Note: Label was removed from bottle for photography purposes only, in order to show the absence of an expiration date or lot number on the bottle.)

Image 6: Regener-Eyes Lite Inactive Ingredients

https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=e7796d0d-13d7-73c3-e053-2995a90a8bde&type=display
(March 5, 2023)

REGENER-EYES LITE
glycerin solution/ drops

Product Information

Product Type	HUMAN OTC DRUG	**Item Code (Source)**	NDC:82305-006
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GLYCERIN (UNII: PDC6A3C0OX) (GLYCERIN - UNII:PDC6A3C0OX)	GLYCERIN	12 mg in 3 mL

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:82305-006-01	3 in 1 BOX	08/24/2022	
1		3 mL in 1 BOTTLE, DROPPER; Type 0: Not a Combination Product		