the dry eye foundation

ALERT - JUNE 8, 2022

Regulatory Compliance Status of Certain Commercial Biologic Dry Eye Drops

IMPORTANT NOTE: This document represents the Dry Eye Foundation's current understanding based on telephone and email communications with the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER), information provided by CBER, information available on the FDA's website, the Code of Federal Regulations, information provided verbally and/or in writing from biologic dry eye drop manufacturers and their suppliers, and information available from biologic dry eye drop manufacturers online. All of our research points to the conclusion that the products described below cannot currently be legally sold in the US. This is echoed by the FDA's existing warning statements about illegally marketed regenerative medicine products that have not been approved. If you have evidence suggesting we may have reached this conclusion in error, we urge you to contact us at 800-484-0244 or info@dryeyefoundation.org.

If you are an eye care provider and believe you may have been incorrectly informed or misled about the regulatory status of a commercial biologic dry eye drop, please contact CBER (see below) with questions or to share your concern about the need for oversight of biologic dry eye drops.

QUESTIONS?
CONTACT THE RELEVANT REGULATORY AUTHORITY

Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Jurisdiction Office
Tel 240-402-7912
Email CBERProductJurisdiction@fda.hhs.gov

SUMMARY

Products	Required steps before legal marketing and sale	Biologic dry eye drops compliance status
Type: Biologic drug Description: Amniotic fluid eye drops and placenta eye drops commercialized for the treatment of dry eye	Standard path: Biologics License Application (BLA) BLA is the biologics equivalent of the NDA for conventional drugs, i.e. approval process involving human clinical trials. This is CBER's "default" position for a biologic drug.	None has conducted a clinical trial *(see clinicaltrials.gov if you wish to confirm)* None has filed a BLA *(call CBER if you wish to confirm)* None has been approved *(call CBER if you wish to confirm)*
	Exception to standard path: Exempt HCT/P Not all HCT/P are exempt from the BLA requirement. Exempt HCT/P are not exempt from *regulation;* they are simply subject to a less burdensome form of regulation than the BLA.	None qualifies for an exemption *(call CBER to determine the factuality of any compliance pathway described to you by a biologic eye drop manufacturer)*

COMMON QUESTIONS

1] What is a Biologic Eye Drop?

A biologic eye drop (BED) is an eye drop that contains a complex protein mixture extracted from human reproductive tissues or secreted liquids, such as placenta, amniotic membrane, or amniotic fluid. These proteins are typically described by BED manufacturers as "cytokines, chemokines and growth factors."

2] What are purported benefits of using a BED?

BEDs are advertised as a "natural" treatment for dry eye disease (both evaporative and aqueous deficient) and blepharitis. Exact claims vary by manufacturer. Key opinion leaders (KOL) and colleagues may report using BEDs for other indications.

3] How are BEDs regulated?

Because the manufacturing process involves taking a tissue or secreted liquid from one individual and manipulating it to create an eye drop used by an unrelated individual, the Public Health and Welfare Act (Title 42) applies. One central purpose of this Act is to prevent the transmission of communicable disease.

4] But BEDs are sterile, so why does Title 42 apply?

Title 42 establishes agents that meet the definition of *biological product*. Proteins – regardless of source – are classified as biological products. The FDA further clarifies that proteins longer than 40 amino acids are regulated; the cytokines, chemokines and other growth factors found in BEDs are longer than 40 amino acids. Therefore, all BEDs are regulated as a biological product.

[Title 42, Chapter 6A, Subchapter II, part F, subpart 1, section 262(i)(1)]

5] How does Title 42 regulate proteins?

Title 42 does not directly regulate the manufacture of biological products. It regulates the marketing and sale of such products through interstate commerce. It is illegal to market or sell a biological product – which includes all BEDs – without a Biologics License in effect for that product.

[Title 42, Chapter 6A, Subchapter II, part F, subpart 1, section 262(a)(1)(A)]

6] Where does the Food and Drug Administration come in?

The Federal Food, Drug and Cosmetics Act (Title 21) created the modern FDA. Once Title 42 has defined a product as a regulated product, the FDA is responsible for enforcing its own set of regulations regarding drug efficacy, safety and purity. When a biologic drug has been approved by the FDA, it will receive a Biologics License.

7] How can I determine if a particular BED has a Biologics License in effect?

You can check on Daily Med (www.dailymed.gov). An FDA approved biologic drug will show "human prescription drug label" and "biologic licensing application" in its listing. Drugs which require FDA approval, and have not been FDA approved, may be declared misbranded if their labeling or packaging make unproven claims about the health benefits of the drug. It is illegal to sell a misbranded product through interstate commerce.

For an example of a Daily Med listing for an approved FDA biologic ophthalmic product, search oxervate (recombinant human nerve growth factor).

8] Why don't Autologous Serum Tears need FDA approval?

Autologous products are made from the patient's own tissues or blood. Because there is no risk of transmission of infectious disease from one individual to another, autologous products do not face the regulatory hurdles imposed on non-autologous products.

Further, AST are created for individuals by compounding pharmacies. They are not marketed or sold through interstate commerce.

9] I recommend a BED made from placenta. The manufacturer says it is an "HCT/P." What does this mean?

HCT/P stands for "human cell or tissue, or cellular- or tissue-derived product." The placenta is a human tissue, therefore a product (in this case, a complex protein mixture) derived from placenta may be classified as an HCT/P.

Certain HCT/P are not considered to be drugs. As such, they need only meet the requirements of Title 42 regarding transmission of communicable disease, and they do not need a human prescription drug label. These products are classified as exempt HCT/P. Manufacturers are eager to obtain exempt status for their products because these products may be legally sold without first having been proven safe and effective through costly clinical trials.

If the manufacturer does not clearly and correctly state that their product is an exempt HCT/P (as opposed to simply an HCT/P), they are using distracting language to imply that any HCT/P does not need to undergo clinical trials to be marketed and sold. A common statement to patient inquiries is that the product is "regulated like a bone or tissue graft."

[For additional explanations of regulation of HCT/P please see the end of this document.]

10] I recommend a BED made from amniotic fluid. The manufacturer says it is regulated as a "non-HCT/P biologic." What does this mean?

The FDA does not use the language "non-HCT/P biologic." This statement likely means that the manufacturer is aware that their BED meets the definition of a biological product under Title 42, but is using distracting language to imply that since HCT/P regulations do not apply to their product, FDA approval is not required at all.

Amniotic fluid is classified as a secreted product, not an HCT/P. Since the presumed active ingredient in amniotic fluid is a complex protein mixture, a BED containing amniotic fluid is regulated under Title 42 as a biological product. This product cannot be marketed or sold for interstate commerce without a Biologics License in effect.

A manufacturer that uses amniotic fluid to make a BED may incorrectly refer to section 361 in the Public Health Service Act (which is Chapter 6A of the Public Health and Welfare Act) as the regulatory code that applies to their product. Section 361 of the PHS Act authorizes the US Secretary of Health and Human Services to take measures to prevent the spread of communicable diseases between states. An HCT/P which meets the criteria for an exempt HCT/P is regulated primarily under section 361, and may be legally marketed as long as appropriate steps are taken to screen donors for specific communicable diseases. However as previously noted, amniotic fluid is not a cell or a tissue, it is a secreted product. Therefore, references to section 361 in this context are irrelevant and misleading.

11] I recommend a product that contains exosomes. What are these and how are they regulated?

Exosomes are cell-derived extracellular vesicles (EV) that contain proteins, lipids, nucleic acids and other metabolic products of cells. They are found abundantly in body fluids such as amniotic fluid.

Cells extracted from a secreted fluid such as amniotic fluid may be considered to be an HCT/P even though the secreted fluid itself is not. Exosomes are not cells and therefore are not an HCT/P.

Since exosomes contain proteins, they are regulated by Title 42. The FDA has released a public information announcement specifically addressing amniotic fluid and exosomes, stating that "As a general matter, exosome products intended to treat diseases or conditions in humans require FDA approval."

https://www.fda.gov/vaccines-blood-biologics/consumers-biologics/consumer-alert-regenerative-medicine-products-including-stem-cells-and-exosomes

12] How would a manufacturer of a BED obtain FDA approval and a Biologics License?

The manufacturer would submit an Investigational New Drug (IND) Application to the FDA and undertake clinical trials. For approval, the FDA requires that the evidence from the clinical trials is sufficient to determine that the drug is effective for its specified indication, can be manufactured with appropriate purity, and that the benefits outweigh the risks.

This is a multi-year process which costs millions of dollars. Failure to obtain a Biologics License is not a paperwork oversight.

https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber

13] The manufacturer of the BED that I recommend states that the processing facility conforms with CGMP. What does this mean?

CGMP means Current Good Manufacturing Practices, which are enforced by the FDA. These describe the minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. An approved drug must be manufactured in a facility that conforms to CGMP. A product which is manufactured in a facility which conforms to CGMP is not automatically an approved drug.

14] What is an HCT/P Establishment?

An HCT/P establishment is a business or facility which has registered with the FDA so that it may obtain and process certain human tissues. You can determine whether a BED manufacturer has an HCT/P facility license by using the link below. An HCT/P establishment will be approved for specific functions. Recovering and processing placenta are not currently listed as possible HCT/P establishment functions.

https://www.accessdata.fda.gov/scripts/cber/CFAppsPub/tiss/Index.cfm

15] I checked Daily Med for a product I recommend, and it has a Human OTC Drug Label. Is this correct?

No. Over-the-counter products are not approved by the FDA, but the FDA regulates them through what is known as a Monograph. The monograph for ophthalmic drug products specifies the allowed active ingredients and combinations of active ingredients [21 CFR Section 349]. It also addresses labeling requirements, including the requirement to state an Indication. The Indication is the medical condition or symptom that the product is intended to alleviate, such as "dry eye."

Proteins are not on the Monograph list of active ingredients. Therefore, a BED cannot be labeled as an OTC product. However, since manufacturers apply for an OTC drug label on what is essentially an honor system, if the manufacturer lists an active ingredient from the Monograph (such as glycerin), and the product package labeling submitted to the FDA conforms to regulatory requirements for OTC labeling, the BED may be incorrectly shown on Daily Med with a marketing status of OTC monograph final.

16] What is a misbranded drug?

Title 21 section 352 defines a misbranded drug as one with labeling that is “false or misleading in any particular.”

17] If a BED I recommend does not have a Daily Med listing, what does this mean?

It most likely means that the manufacturer is marketing and selling a product of which the FDA is completely unaware. Since the BED is advertised to patients and providers as a treatment for dry eye disease, it is considered a drug. It could be classified as misbranded because there is no proof that it is safe and effective for this purpose.

Manufacturers of BEDs may make explicit therapeutic claims on their web sites but deliberately eliminate any mention of those claims on the actual product packaging. You should obtain and carefully examine the packaging of any BED that you recommend. You may discover that there is no reference to “dry eye” on the box or package insert. The box may be markedly different from the image of the box shown on Daily Med (if any). The package insert may include disclaimers about the biological activity of the contents or the potential for transmission of communicable disease.

Prohibited acts under Title 21 Section 331 include the receipt of a misbranded product through interstate commerce, which may apply to you if you are stocking a BED for sale to your dry eye patients.

18] If BEDs are not approved by the FDA, why are they advertised?

The FDA has no authority to review advertisements in professional journals, on the internet, or in other direct-to-consumer media before they are released. They can notify a manufacturer that a particular advertisement violates the law, but only after it has appeared.

For a good reference see this:
https://www.fda.gov/drugs/prescription-drug-advertising/prescription-drug-advertising-questions-and-answers#control_advertisements

19] What about the bottles? Does the FDA regulate those too?

Yes. There are specific requirements for liquid ophthalmic preparations. The containers must either contain one or more harmless substances that will inhibit the growth of microorganisms (ie preservatives), or utilize a container that minimizes the hazard of injury resulting from contamination during use (eg single-use vials, preservative-free multi-dose dropper bottles). Non-preserved products must also be labeled as to safe duration of use and contain other necessary warnings (such as storage temperature).

The currently marketed BEDs are liquid ophthalmic preparations that contain no preservatives. The bottle is a standard eye drop bottle without a multi-dose preservative-free dropper. Manufacturers state that most BEDs may be stored at room temperature, and need not be discarded until 90 days after opening. This allows for the possibility of significant colonization of the BED liquid in the bottle, and a risk of injury related to repeated inoculation of contaminated eye drops onto the ocular surface.

[Title 21, Chapter 1, subchapter C, part 200, subpart C, section 200.50(b)]

20] Could a BED derived from placenta be an exempt HCT/P?

No. An HCT/P must meet a number of specific criteria to be classified as exempt. Two of these criteria relate to how the donor tissue is processed (minimal manipulation), and to the HCT/P’s intended use in the recipient (homologous use).

Minimal manipulation means that the processing required to create the HCT/P does not alter the relevant characteristics of the tissue as it existed and functioned in the donor. To extract proteins from placenta, the placenta

must be lyophilized (freeze dried), ground, and then undergo a protein extraction process, which destroys the placental tissue. This is considered more than minimal manipulation.

Homologous use means that the HCT/P performs the same basic function or functions in the recipient as in the donor (for example, a bone graft is used to replace damaged bone). The placenta is a solid organ whose basic function is to support the development of the fetus. An extracted placental protein mixture cannot perform this basic function, and is thus not a homologous use.

Proteins derived from placenta are therefore not an exempt HCT/P and are regulated by the FDA as a biologic drug.

[Title 21, Chapter 1, subchapter L, part 1271, subpart A, section 1271.10]

21] If ProKera is legal, won't a BED from amniotic membrane be legal too?

ProKera is produced from amniotic membrane. It is classified as an exempt HCT/P, which means that it did not have to undergo clinical trials. The reasons for the exemption are as follows:

To make ProKera, amniotic membrane is processed to preserve it and then it is packaged in sheets. This is considered minimal manipulation.

Amniotic membrane's basic structural function is to serve as an environmental barrier. When used in ProKera, amniotic membrane performs the same function. This is considered homologous use.

Conversely, to extract proteins from amniotic membrane the tissue would need to be lyophilized (freeze dried), ground, and then undergo a protein extraction process. The tissue has had more than minimal manipulation. The protein extract does not retain the tissue's original structural function as a physical barrier, which is non-homologous use. Proteins derived from amniotic membrane are therefore not an exempt HCT/P and are regulated by the FDA as a biologic drug.

[Title 21, Chapter 1, subchapter L, part 1271, subpart A, section 1271.10]

Examples of amniotic membrane in the production of exempt and non-exempt HCT/P are specifically described by the FDA in a guidance document on regulatory considerations for HCT/P (see pages 11 and 19 of the linked document).

https://www.fda.gov/media/109176/download

22] I purchase a BED and sell it to my patients in my office. Am I breaking the law?

Unfortunately, yes. Title 21 Section 331(c) defines as a prohibited act, "The receipt in interstate commerce of any…drug…that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise." Because no BED has FDA approval, all BEDs are considered misbranded if they are marketed for the treatment of dry eye disease or other ocular surface conditions. Even if you gave the BED away for free, because you received it in interstate commerce you are breaking the law.

Somewhat like Al Capone getting sent to jail for tax evasion, selling a misbranded drug product in your office may place you at risk for legal action unrelated to the quality of your care. You should discuss the fact that you are selling a non-approved drug in your office with your malpractice carrier and general business insurance carrier before doing so.

23] I recommend that my patients purchase a BED directly from the manufacturer or from a fulfillment pharmacy. Am I breaking the law?

The FDA's enforcement authority primarily lies with controlling what drugs are marketed and sold. They aren't going to come after you individually, although you may be drawn in to their action against a manufacturer.

If a patient is harmed through use of a BED, or even alleges harm, the fact that it was not FDA approved may seriously compromise your defense.

Your State Professional Board and your malpractice carrier may also have concerns about your clinical care. If you are representing a BED as a safe and effective treatment for dry eye disease without clearly informing your patients that the product has not been assessed by the FDA, and that this represents your own opinion based on your own clinical experience, this omission may represent a lack of informed consent. Lack of informed consent is a common cause of malpractice litigation.

24] I prescribe drugs for unapproved uses all the time and this is not illegal, unethical or dangerous to my patients. Why are BEDs any different?

There is a profound difference between prescribing an FDA approved drug for an unapproved indication (off label) and encouraging your patients to purchase and use a biologic drug that has not been approved by the FDA for any indication.

Off label prescribing is not a prohibited act, The medical standard of care determines whether your prescribing decision was reasonable and prudent.

Manufacturing, marketing and selling a BED for the treatment of dry eye disease without a Biologics License in effect are prohibited acts.

Purchasing and re-selling an unapproved biologic drug are prohibited acts. Your State Board may have rules of professional conduct related to this issue.

Recommending that your patients purchase a BED through a manufacturer or pharmacy may violate the fine print of your malpractice policy, leaving you without coverage if a patient later claims harm due to use of the BED.