Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact the office of Combination Products at 301-796-8930 or combination@fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Combination Products (OCP)

March 2022
Combination Products

Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4 Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances
and/or
Office of Policy
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 66, Room 5431
Silver Spring, MD 20993-0002
Email: CDRH-Guidance@fda.hhs.gov
https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/guidance-documents-medical-devices-and-radiation-emitting-products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Combination Products (OCP)

March 2022
Combination Products

Contains Nonbinding Recommendations

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4 Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to provide information to applicants and manufacturers regarding compliance with the requirements in part 4 (21 CFR part 4) for ophthalmic drugs[1] packaged with eye cups, eye droppers, or other dispensers. This guidance applies to products with pending applications,[2] approved products, and products marketed pursuant to section 505G of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355h) without an approved application under section 505 of the FD&C Act (21 U.S.C. 355) (commonly referred to as over-the-counter (OTC) monograph drugs).

FDA is implementing this guidance without prior public comment because the Agency has determined that prior public participation is not feasible or appropriate (21 U.S.C. 371(h)(1)(C)(i) and 21 CFR 10.115(g)(2)). We made this determination because FDA needs to communicate its compliance policy in a timely manner given the urgency of these issues following the decision of the U.S. Court of Appeals for the District of Columbia Circuit in *Genus Medical Technologies LLC v. U.S. Food and Drug Administration*. Although this guidance is immediately in effect, FDA will consider all comments received and determine whether revisions to the guidance document are appropriate (§ 10.115(g)(3)).

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

[1] The term *drug* as used in this guidance refers to both human drugs and biological products unless otherwise specified.

[2] For the purposes of this guidance, pending applications include applications on which FDA has taken an action that is not an approval action and that are not currently pending review before the Agency (i.e., applications that have been tentatively approved or applications that have received a complete response letter) and applications currently pending review before the Agency (including supplements to approved applications).

II. BACKGROUND

In accordance with § 200.50(c) (21 CFR 200.50(c)), eye cups, eye droppers, and other dispensers intended for ophthalmic use (collectively referred to as ophthalmic dispensers) have been regulated as drugs when packaged together with the ophthalmic drug with which they were intended to be used. Regulating ophthalmic dispensers as drugs is a departure from how FDA regulates other devices that are packaged with the drugs with which they are intended to be used. Specifically, when a device is packaged together with the drug with which it is intended to be used, FDA regulates that drug and the device together as a combination product (see § 3.2(e) (21 CFR 3.2(e)).

On April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit issued its decision in *Genus Medical Technologies LLC v. U.S. Food and Drug Administration*, 994 F.3d 631 (D.C. Cir. 2021). The *Genus* court stated "[e]xcepting combination products, . . . devices must be regulated as devices and drugs — if they do not also satisfy the device definition — must be regulated as drugs."[3] In implementing this decision, FDA has determined that the language in § 200.50(c) indicating that ophthalmic dispensers are regulated as drugs when packaged with ophthalmic drugs is now obsolete, because these articles meet the *device* definition. Therefore, FDA intends to regulate these products as drug-led combination products composed of a drug constituent part that provides the primary mode of action and a device constituent part (an ophthalmic dispenser). Because the drug constituent part provides the primary mode of action, generally the Center for Drug Evaluation and Research (CDER) will have primary jurisdiction over these products.[4]

III. DISCUSSION

Before the *Genus* decision, ophthalmic dispensers packaged together with the ophthalmic drug with which they were intended to be used were regulated as drugs. Therefore, products consisting of an ophthalmic drug packaged with an ophthalmic dispenser were not regulated as combination products as defined in § 3.2(e) and were not subject to the requirements in part 4. However, following the *Genus* decision, an ophthalmic dispenser that meets the definition of *device* in section 201(h) of the FD&C Act (21 U.S.C. 321(h)) and that is packaged together with an ophthalmic drug is now regulated as a device constituent part (see § 3.2(e)). This change impacts products subject to pending applications, approved products, and OTC monograph drugs.

[3] For more information on FDA's implementation of the *Genus* decision, see "Genus Medical Technologies LLC Versus Food and Drug Administration; Request for Information and Comments," 86 FR 43553 (Aug. 9, 2021).
[4] Some of these combination products may consist of an ophthalmic dispenser packaged with a biological product that would be assigned to the Center for Biologics Evaluation and Research (CBER) if marketed on its own. In these instances, CBER will have primary jurisdiction over the combination product.

A. Products Subject to an Approved Application and Products Marketed Under Section 505G of the FD&C Act

We recognize that some applicants and manufacturers may need to develop policies and procedures necessary to comply with the requirements in part 4. Therefore, for a period of 12 months following the publication of this guidance, FDA generally does not intend to take action with respect to noncompliance with part 820 (21 CFR part 820) as described in part 4, subpart A, with respect to ophthalmic products that were not previously regulated as combination products because of the now obsolete language in § 200.50(c). We believe that this 12-month period provides these applicants and manufacturers sufficient time to develop and implement the policies and procedures necessary to comply with these newly applicable requirements.

As described in the FDA guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017),[5] although pharmaceutical development focuses on drug considerations, many pharmaceutical development practices (for example, Quality-by-Design principles),[6] if broadened to take into account the other constituent parts of combination products and how they interrelate, can be leveraged and built upon when demonstrating compliance with part 4 requirements for a combination product. For example, it would be appropriate to leverage existing data in developing a design history file if a combination product is subject to design control requirements but has not been developed under design controls. Existing specifications may become part of the required design output documentation. Similarly, testing performed before distribution of the combination product may be included as documentation of design verification and validation.

The applicant or manufacturer of the combination product is responsible for assembling available information and assessing what, if any, additional information and evidence may be needed (such as additional testing or documentation of the design control activities) to address all aspects of design control that are needed to support the manufacture of the product as currently marketed, ensure its safety and effectiveness, and support any future changes to that product.[7] Applicants and manufacturers are not expected to retroactively prepare certain parts of the development plan or conduct design review meetings for the product as currently marketed because the development stages that these activities would support have already occurred. However, they should put a design and development plan in place, and they should have procedures for design review meetings in place to support future design activities such as future design changes.

Additionally, some ophthalmic products that were not previously regulated as combination products because of the now obsolete language in § 200.50 incorporate lower-risk device constituent parts, for example, eye dropper bottles/ampules that administer the drug directly to the eye. The Agency is evaluating the application of part 820 quality system (QS) requirements to combination products that include such constituent parts. Until FDA has further considered the application of these requirements to these combination products, the Agency generally does

[5] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[6] See FDA guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).
[7] § 820.30.

not intend to take action with respect to noncompliance with any applicable part 820 requirements for these ophthalmic products. When the Agency publishes its current thinking on application of part 820 requirements to these combination products, FDA will also address its timing expectations for applicants and manufacturers of such combination products to come into compliance with any applicable part 820 requirements. If you have questions regarding whether your combination product includes such a device constituent part, we recommend that you contact CDER's Office of New Drugs or Office of Generic Drugs, as appropriate.

However, if you submit a supplement to an approved application for an ophthalmic product that was previously not regulated as a combination product due to the now obsolete language in § 200.50, the information in subsection III.B below may apply to the supplement if the supplement includes a change related to product quality or to the device facility information (e.g., a finished product manufacturing site change, a chemistry, manufacturing, and controls-related change, or a new device constituent part).

In addition, for a period of 12 months following the publication of this guidance, FDA does not intend to take action with respect to the requirements set forth in part 4, subpart B (postmarketing safety reporting requirements for combination products), against any applicant (as defined in 21 CFR 4.101) of an ophthalmic product that was not previously regulated as a combination product because of the now obsolete language in § 200.50.[8]

B. Products Subject to a Pending Application

Generally, FDA intends to request that you provide an updated Form FDA 356h to your pending application, indicating that the product is a combination product and identifying all facilities involved in the manufacturing of the combination product, including all facilities involved in the manufacturing of each constituent part and all facilities responsible for the disposition (e.g., release) of the combination product.[9] Any additional impact on products subject to pending applications currently under review would depend on the risk profile of the product, the type of application, and the information that was already provided in your application. The following circumstances may arise during the review of your pending application:

FDA may determine that, based on the risk profile of your combination product, information to demonstrate compliance with any applicable device QS regulation requirements is most appropriately assessed during inspection following approval; in such cases, this information should not be submitted in the application but must be available upon inspection to demonstrate your compliance with part 4.[10]

---

[8] Information on postmarketing safety reporting requirements for combination products is available at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

[9] FDA also recommends that applicants review other guidances for industry that apply to CDER-led drug-device combination products to determine if any additional information should be submitted in the application.

[10] 21 CFR part 4. See section III.A for a description of any enforcement discretion that may be applicable to inspections that take place after approval.

In other situations, FDA may determine that, based on the risk profile of your combination product, information to demonstrate compliance with the device QS regulation should be submitted for review as part of the quality assessment of your application. If you are using a drug current good manufacturing practice-based operating system, in addition to demonstrating compliance with 21 CFR parts 210 and 211, you also should submit summary information to describe how your firm has applied each applicable provision in the device QS regulation described in § 4.4(b), including descriptions of the specific procedures and activities conducted by your firm and references to the types of protocols used by your firm for each activity. If you have not submitted this information, you may be asked to submit additional information in response to an information request.[11]

Also, FDA may determine that a pre-approval inspection of the facility performing combination product manufacturing is warranted before your pending application can be approved. However, given what has been known generally about the products subject to this guidance, for pending submissions of a product subject to this guidance, FDA anticipates that pre-approval assessment of your compliance with any applicable QS regulation requirements generally will not need to include facility inspection against these requirements. Rather, FDA anticipates that assessment of information demonstrating compliance with such requirements generally will be covered as described above.

FDA's review of a pending application for a combination product generally does not include a review of the applicant's ability to comply with the postmarketing safety reporting requirements in part 4, subpart B. However, applicants must comply with these requirements if their application is approved. We recognize that some applicants may need additional time to develop and implement policies and procedures to comply with these part 4 requirements. Thus, for approved products subject to these requirements, FDA generally does not intend to take action with respect to noncompliance with these part 4 requirements for a period of 12 months after publication of this guidance.

[11] See discussion of design control in section III.A.