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Update on FDA regulation of ophthalmic combination products

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Ophthalmic products are regulated under quality standards published in the Code of Federal Regulations (CFR), United States Pharmacopeia (USP), and various US Food and Drug Administration (FDA) guidance. Application of these standards has recently been affected by the legal requirement for the FDA to standardize the regulatory approach to ophthalmic products whose components are considered devices. The agency communicated the update through a guidance outlining the phase-in of the new regulatory requirements and their application to different product types. This article discusses the quality standards for ophthalmic combination products and evaluates their application to marketed and developmental products within the framework of recent regulatory requirements.

Keywords – combination products, device, ocular, ophthalmic

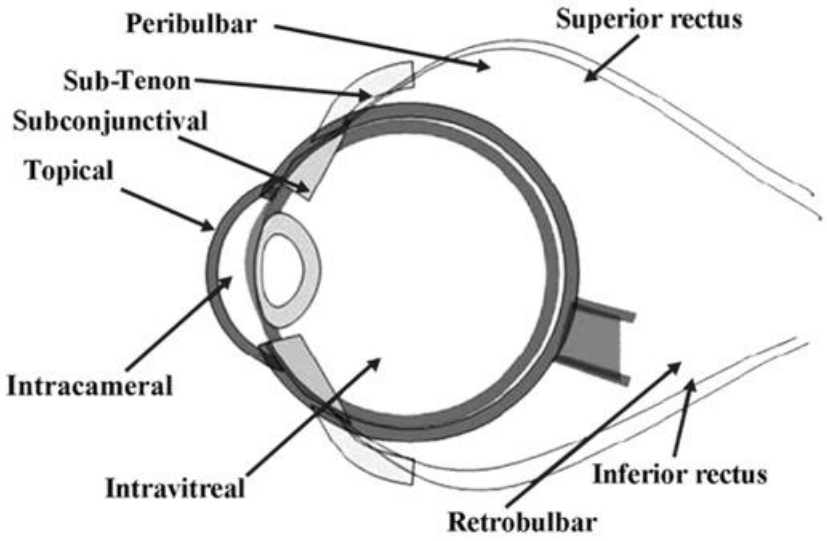
Introduction

Ophthalmology, the diagnosis and treatment of diseases and disorders of the eye, has been documented since ancient times.[1] For centuries, the importance of and fascination with the eye has led to significant advancements in the field. This is no less true today, with a growing interest in the research and development of ophthalmic products. Development of ophthalmic products must take into consideration new regulatory requirements articulated through FDA guidance. Through review of the requirements, as well as selected example applications presented as case studies, the authors will illustrate the application of these new requirements to ophthalmic combination products in different scenarios.

USP quality tests and packaging considerations

Ophthalmic drug products include a range of dosage forms such as solutions, suspensions injections, and implants placed through one of several ocular routes of administration (**Figure 1**). USP General Chapter 771 (USP 771) provides

Figure 1. Examples of ocular routes of administration



Source: United States Pharmacopeia[1]

guidance for quality tests for controlling such ophthalmic drug products.[2] The chapter includes both universal and specific tests for quality control of ophthalmic products, similar to the specifications in the International Council for Harmonisation's (ICH's) Guidance Q6A.[3] In addition to the quality attributes covered in USP 771, performance tests (dissolution/drug release) are detailed in USP 1771 for ophthalmic products.

Universal tests in USP 771 are applicable to all ophthalmic drug products, irrespective of the dosage form (**Table 1**, p. 3). Four of these tests – description, identification, assay, and impurities – are also included as universal tests in ICH Q6A. The description of these tests in the general chapter includes guidance for acceptance criteria. There are also directions for applying the tests based on route of administration, dosage forms, and packaging configurations (i.e., single-unit vs. multidose containers). Specific tests for ophthalmic drug products included in USP 771 are presented in **Table 2** (p. 3).

Performance tests for ophthalmic products, as detailed in USP 1771, include dissolution and drug release tests according to USP 711 and USP 724, respectively. These methods should be developed with test conditions that simulate the method of dose administration. As with performance tests for other types of drug products, the FDA requires data to demonstrate the discriminating ability of the method.[4] There are a range of dosage forms for

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Table 1. Ophthalmic drug products: Universal tests per USP 771

Universal test	Additional ICH and/or USP reference
Description	ICH Q6A
Identification	ICH Q6A; USP General Notices, 5.40
Assay	ICH Q6A; USP General Chapters 81, 621, 1065
Impurities	ICH Q6A
pH	USP 791
Osmolarity	USP 785
Particulate and foreign matter	USP 788, 790, and 1790
Sterility	USP 71
Antimicrobial preservatives	USP 51, 341
Bacterial endotoxins	USP 85
Uniformity of dosage units	USP 905
Container contents	USP 755
Leachables and extractables	USP 381, 660, 661, 661.1, 661.2, 1663, 1664
Container-closure integrity	USP 1207

Table 2. Ophthalmic drug products: Specific tests per USP 771

Specific test	Supplemental test information
Viscosity	SP 911, 912, 913. Viscosity is included based on the type of dosage form and whether changes in product viscosity will affect its performance.
Antioxidant content	Test to be included if antioxidants are present in the drug product, unless detected by another method.
Resuspendability/ redispersibility	Test to be included for ophthalmic suspensions.
Particle size/particle size distribution	USP 429. Test to be included for ophthalmic suspensions and emulsions.
Drop size	Test to be included for ophthalmic drug products dispensed as drops and is typically evaluated during development.
Added substances	Test is typically evaluated during development.

results in the use of noncompendial apparatuses and test parameters. Justification for the selection of the method parameters and supporting method validation data will be required in support of a marketing application.

The range of dosage forms also means ophthalmic drug products may be presented in various packaging configurations. The FDA's guidance on closure systems for packaging human drugs and biologics offers direction on the information, study data, and compliance requirements that should be provided in support of ophthalmic drug product container closure systems.[5] The information and/or data should address the following:

- **Protection –** Needed to demonstrate the capability of the container closure system to provide protection from light, solvent loss/leakage, microbial contamination, and reactive gases.
- **Compatibility –** Needed to demonstrate the compatibility of the container closure system for liquid-based dosage forms such as stability data, including leachables.
- **Safety –** USP testing, including USP biological reactivity tests, extraction profiles, and toxicological evaluation, should be completed as needed.
- **Performance –** Data (e.g., drop size) for the ophthalmic drug product's container closure system may need to be evaluated.

In addition, a uniform color-coding system has been established for the caps and labels of these topical ocular medications based on the voluntary cooperation of the pharmaceutical industry, the FDA, and the American Academy of Ophthalmology (AAO). This system was implemented to address patient safety, based on reports of serious adverse events to the AAO and National Registry of Drug-Induced Ocular Side Effects.[6]

FDA regulation of ophthalmic products

Regulatory applications for ophthalmology products fall under the jurisdiction of the FDA's Division of Ophthalmology in the Office of Specialty Medicine at the Center for Drug Evaluation and Research (CDER). In 2022, the FDA approved eight new ophthalmic products, including an ophthalmic gel indicated for ocular surface anesthesia; an ophthalmic solution for reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension; the first bispecific antibody for treatment of wet age-related macular degeneration; and drug-eluting contact lenses indicated for the treatment of ocular itch.[7] This is indicative of the larger trend of growth in the research and development of ophthalmic products, with the global ophthalmic drugs market expected to see a compound annual growth rate of 7.7% from 2022 to 2030.[8]

Regulatory update for ophthalmic products as combination products

Ocular drug delivery has evolved in recent decades from widely used eye drops administered as a solution from a dropper bottle to more elaborate systems such as drug-eluting contact lenses for improving efficacy or reducing dosing frequency. The regulatory requirements for such systems have had to evolve as well to ensure that product quality and performance are confirmed through appropriate tests and controls, and patient safety is maintained.[9] In addition, some commonly used and well-established drugs for ophthalmic delivery started being packaged with eye cups, eye droppers, or other dispensers essential to the accurate dosing and precise application at the appropriate eye segment. As expected, the regulatory requirements had to be adapted to ensure appropriate characterization of such systems.

In April 2021, the US Court of Appeals for the District of Columbia Circuit (DCC) issued the Genus decision in which it said the FDA cannot classify as a drug any product that meets the definition of device, "excepting combination products, . . . devices must be regulated as devices, and drugs – if they do not also satisfy the device definition – must be regulated as drugs."[10] Before that decision, certain types of products that met the drug definition and may also have met the device definition, including all contrast imaging agents, were regulated as drugs to ensure they were regulated consistently under CDER authority and in accordance with a previous 1997 DCC ruling (Bracco Diagnostics Inc. v. Shalala, 963 F. Supp. 20). After the Genus decision, the FDA had to transition some approved products from drug to device status. Therefore, in March of 2022, the agency issued guidance on compliance with 21 CFR Part 4 for certain ophthalmic products[11] to provide information to applicants and manufacturers regarding ophthalmic drugs packaged with eye cups, eye droppers, or other ophthalmic dispensers, where those articles meet the device definition. In doing so, the agency clarified its intention 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)."[11] The guidance applies to approved products, those with pending applications, and over-the-counter marketed monograph drugs.

Impact of the regulatory updates

Approved applications and marketed products

Products already approved or marketed when the 21 CFR Part 4 compliance guidance was issued are expected to be compliant by the end of February 2023. FDA granted a 12-month period for the affected applicants and manufacturers to develop appropriate policies and procedures that would ensure compliance with the new requirements.

For single-entity combination products and copackaged combination products, 21 CFR Part 4 identifies two ways to demonstrate compliance with continuing good manufacturing practice (cGMP) requirements:[9]

- **Option A –** Demonstrate compliance with all cGMP regulations applicable to each of the constituent parts included in the combination product, or
- **Option B –** Implement a streamlined approach for combination products that include a drug and a device by demonstrating compliance with either the drug cGMPs (21 CFR Parts 210 and 211) or the device quality system (QS) regulation (21 CFR Part 820) as well as compliance with specified provisions from the other of these two sets of cGMP requirements.

The guidance notes that compliance with 21 CFR Parts 600 through 680 is required for combination products that include a biological product and compliance with 21 CFR Part 1271 is required for those that include human cells, tissues, and cellular- and tissue-based products.

If option B (streamlined approach) is chosen, the applicant or manufacturer of the combination product is responsible for assembling, assessing, and identifying the available and any missing information and appropriately selecting to demonstrate compliance with either a drug cGMP-based streamlined approach in accordance with 21 CFR 4.4(b)(1) or a device QS regulation-based streamlined approach in accordance with 21 CFR 4.4(b)(2), as summarized in **Table 3**. There is no requirement to choose a streamlined approach based on the constituent part that provides the primary mode of action of the combination product. It is expected that any choice is sufficiently justified. The manufacturing process and activities undertaken at a facility are generally a key consideration in making this assessment. When in doubt, discussions with the agency are encouraged.

The FDA will carefully consider the risk associated with device constituent parts and plans to address low-risk device constituent parts (e.g., eye dropper bottles/ampules that administer the drug directly to the eye) by evaluating the application of 21 CFR Part 820 QS requirements to combination products that include such constituent parts. However, the agency does not intend to act on noncompliance with any applicable Part 820 requirements for these low-risk products[11] until it has issued guidance on the topic.

For the affected products that are not considered low risk but have not been developed as combination products, and therefore have not been developed under design controls, it is acceptable to use existing data to develop a design

Table 3. Demonstrating 21 CFR Part 4 compliance for single-entity combination products and copackaged combination products

Option A – No suboptions
Demonstrate compliance with all cGMP regulations applicable to each of the constituent parts
Option B – With suboptions
Suboption 1
Drug cGMP-based streamlined approach in accordance with 21 CFR 4.4(b)(1), i.e., drug cGMPs and specified provisions from the device QS regulation • 21 CFR 820.20 Management responsibility • 21 CFR 820.30 Design controls • 21 CFR 820.50 Purchasing controls • 21 CFR 820.100 Corrective and preventive action • 21 CFR 820.170 Installation • 21 CFR 820.200 Servicing
Suboption 2
Device QS regulation-based streamlined approach in accordance with 21 CFR 4.4(b)(2), i.e., device QS regulation and specified provisions from the drug cGMPs • 21 CFR 211.84 Testing and approval or rejection of components, drug product containers, and closures • 21 CFR 211.103 Calculation of yield • 21 CFR 211.132 Tamper-evident packaging requirements for OTC human drug products • 21 CFR 211.137 Expiration dating • 21 CFR 211.165 Testing and release for distribution • 21 CFR 211.166 Stability testing • 21 CFR 211.167 Special testing requirements • 21 CFR 211.170 Reserve samples

CFR, Code of Federal Regulations; **cGMP,** current good manufacturing practice; **OTC,** over the counter; **QS,** quality system.

Source: Food and Drug Administration[9]

history. Current specifications may be included in the design output documentation. Also, release, stability and performance testing of the combination product may be included in the design verification and validation documentation. However, a design and development plan must be generated to support potential future design modifications.

Pending applications

Manufacturers and applicants of ophthalmic products that are still under development but are affected by the regulatory update[11] are expected to submit an updated Form 356h, wherein the product is identified as a combination product and all the manufacturing and release facilities for all constituents are listed. These products are also expected to be compliant with 21 CFR Part 4 by the end of February 2023. Similar to an approved or marketed product, the risk profile of the combination product will be essential for defining the type of information required to demonstrate compliance with 21 CFR Part 4. The two options and suboptions from Table 3 apply to pending applications as well. In addition, if the combination product is subject to design control requirements because development is ongoing, development plan and design control activities, along with design review meetings, should become part of the program.

For combination products with a low-risk profile, compliance with any applicable device QS regulation requirements will likely be assessed by the FDA during inspection following approval. For all other combination products, information to demonstrate compliance with the device QS regulation should be submitted as part of the quality assessment of the application. Whether a preapproval inspection of the facility performing combination product manufacturing will be required or not will be determined by the FDA based on the information provided by the applicant and the risk profile of the product.

Applications of the ophthalmic products regulatory update

Before the 2022 ophthalmic products policy guidance was issued, the impact of the Genus ruling was reflected in the FDA's review of some ophthalmic products. For example, the October 2021 approval documentation for Vuity (pilocarpine HCl ophthalmic solution, 1.25%) indicated that the product was reclassified as a drug-device combination product according to the Genus decision. In addition, a Center for Devices and Radiological Health (CDRH) QS-GMP consultation was deemed not necessary because of the simplicity of the container closure system.[12] Similar reclassification is evident in the review documentation for Omlonti (omidenepag isopropyl ophthalmic solution, 0.002%; NDA 215092), which was approved in September 2022.[13] The quality review further stated that a CDRH QS review and facility consultation was not needed and that information demonstrating compliance with the device QS regulations (21 CFR Part 4) would be assessed during inspection (rather than review), based on the risk profile of the combination product.

Ophthalmic products in advanced stages of development have been similarly affected by the policy guidance.[11] Reclassification of such products as combination products resulted in changes to the information required in their marketing applications. Two examples of the impact of the reclassifications as

combination products are discussed below. Note that identifying information for the products in the examples is not provided for confidentiality reasons.

The marketing application for Product 1 was submitted before issuance of the guidance. The product was not developed as a combination product although the container closure system had significant device elements, such as dose control and dose placement. Therefore, although the dossier was submitted as a conventional (noncombination) drug product, available device-type information (such as biocompatibility, performance characteristics, and accelerated aging data) was included in the container closure sections of the electronic common technical document (Sections 3.2.P.2.4 and 3.2.P.7). The choice of development and submission pathway was based on the new drug application (NDA) sponsor's preference and experience with the relevant regulatory review division. Following issuance of the guidance, the FDA requested additional information during review of the NDA, including design elements, additional performance data for the device-like container closure system, and information supporting conformance of product manufacture to applicable sections of quality risk management regulations (21 CFR Parts 4 and 820). The information provided seemed to satisfy the agency requests.

Product 2's container closure was a much simpler dropper-type configuration compared with Product 1 and was initially documented as a simple, sterile vial, but reclassified as a device after the guidance was issued. The development activities occurred at approximately the same time as the release of the FDA's position on future ophthalmic products (based on the Genus ruling). Because of the timing, the NDA sponsor was able to include dose delivery and performance data as well as vendor qualification and biocompatibility information in appropriate sections of the NDA. This supplemental documentation for the container closure system helped fulfill the requirements of 21 CFR Parts 4 and 820. Under an agreement with the FDA, study data for detailed human factors were omitted because of the simplicity of the container closure system and its similarity to containers already approved for noncombination products.

Summary and conclusion

Ophthalmic drug products include a variety of dosage forms, both common and novel, and are presented in various packaging configurations. The framework for applicable development activities is delineated in the relevant USP chapters, ICH guidelines, and FDA guidances. Development must be planned in a systematic and strategic manner to ensure consistent product quality, performance, and safety. In a March 2022 regulatory update for certain ophthalmic products packaged with dispensers,[11] the FDA clarified that ophthalmic dispensers are now regulated as devices, and the drug and device together are regulated as a combination product. This regulation has become a critical consideration for development and postapproval activities and all

affected applicants or manufacturers are expected to be compliant with 21 CFR Part 4 by the end of February 2023. Reviewing, understanding, and satisfying the regulatory guidelines for currently marketed products and applications in development are required for NDA sponsors and is dependent on the product's risk profile. The examples cited in this article illustrate how products may be affected differently by this regulatory update, thereby emphasizing the importance of a multidisciplinary risk assessment approach in order to identify appropriate development and regulatory path.

Acronyms and abbreviations

AAO, American Academy of Ophthalmology**; CDER,** Center for Drug Evaluation and Research**; CDRH,** Center for Devices and Radiological Health; **CFR,** Code of Federal Regulations; **cGMP,** current good manufacturing practices; **FDA,** [US] Food and Drug Administration; **ICH,** International Conference on Harmonization; **NDA,** new drug application; **QS,** quality system; **USP**, United States Pharmacopeia.

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