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# Quality Considerations for Topical Ophthalmic Drug Products Guidance for Industry

## ***DRAFT GUIDANCE***

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**December 2023  
Pharmaceutical Quality/CMC**

**Revision 1**

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# Quality Considerations for Topical Ophthalmic Drug Products Guidance for Industry

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**December 2023  
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*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

**TABLE OF CONTENTS**

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>II.</b>	<b>MICROBIOLOGICAL CONSIDERATIONS.....</b>	<b>2</b>
<b>A.</b>	<b>Product Sterility .....</b>	<b>2</b>
<b>B.</b>	<b>Multidose Drug Products .....</b>	<b>3</b>
<b>III.</b>	<b>VISIBLE PARTICULATE MATTER.....</b>	<b>4</b>
<b>IV.</b>	<b>EXTRACTABLES AND LEACHABLES.....</b>	<b>5</b>
<b>A.</b>	<b>Extractables Studies.....</b>	<b>5</b>
<b>B.</b>	<b>Leachables Studies.....</b>	<b>6</b>
<b>C.</b>	<b>Safety Thresholds.....</b>	<b>6</b>
<b>V.</b>	<b>IMPURITIES AND DEGRADATION PRODUCTS .....</b>	<b>7</b>
<b>A.</b>	<b>NDA, ANDA, and OTC Monograph Drugs.....</b>	<b>7</b>
<b>B.</b>	<b>BLAs.....</b>	<b>8</b>
<b>VI.</b>	<b>IN VITRO DRUG RELEASE/DISSOLUTION TESTING FOR QUALITY CONTROL .....</b>	<b>9</b>
<b>VII.</b>	<b>CCS DESIGN AND DELIVERY AND DISPENSING CHARACTERISTICS .....</b>	<b>9</b>
<b>A.</b>	<b>CCS Design.....</b>	<b>9</b>
1.	<i>Tamper-Evident Packaging .....</i>	<i>9</i>
2.	<i>Tips.....</i>	<i>10</i>
3.	<i>Torque Specifications.....</i>	<i>10</i>
4.	<i>Color Coding .....</i>	<i>10</i>
<b>B.</b>	<b>Delivery and Dispensing Characteristics .....</b>	<b>10</b>
1.	<i>Unit Dose Containers .....</i>	<i>10</i>
2.	<i>Multidose Containers.....</i>	<i>10</i>
<b>VIII.</b>	<b>STABILITY.....</b>	<b>11</b>
<b>A.</b>	<b>Container Orientation During Storage .....</b>	<b>11</b>
<b>B.</b>	<b>Water Loss.....</b>	<b>12</b>
<b>C.</b>	<b>Freeze/Thaw Study for Emulsions and Suspensions .....</b>	<b>12</b>
<b>D.</b>	<b>In-Use Stability Studies .....</b>	<b>13</b>
<b>IX.</b>	<b>GLOSSARY.....</b>	<b>13</b>

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1 **Quality Considerations for Topical Ophthalmic Drug Products**  
2 **Guidance for Industry<sup>1</sup>**  
3

4  
5 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
6 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
7 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
8 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
9 for this guidance as listed on the title page.  
10

11  
12  
13  
14 **I. INTRODUCTION**  
15

16 This guidance discusses certain quality considerations for ophthalmic drug products<sup>2</sup> (i.e., gels,  
17 ointments, creams, and liquid formulations such as solutions, suspensions, and emulsions)  
18 intended for topical delivery in and around the eye. Specifically, the guidance discusses:  
19

- 20 • Microbiological considerations.
- 21
- 22 • Approaches to evaluating visible particulate matter, extractables and leachables, and  
23 impurities and degradation products.
- 24
- 25 • Use of in vitro drug release/dissolution testing as an optional quality control strategy for  
26 certain ophthalmic dosage forms.
- 27
- 28 • Recommendations for design, delivery, and dispensing features of container closure  
29 systems (CCSs).<sup>3</sup>
- 30
- 31 • Recommendations for stability studies.  
32

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<sup>1</sup> This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

<sup>2</sup> The term *drug product*, as used in this guidance, refers to drugs approved pursuant to new drug applications (NDAs) and abbreviated new drug applications (ANDAs) under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act; 21 U.S.C. 355); biological products licensed under section 351(a) or (k) of the Public Health Service Act (PHS Act; 42 U.S.C. 262(a) or (k)) that are regulated as drugs; and other drugs that, while also subject to CGMP requirements, are not marketed pursuant to an approval or licensure, including products marketed pursuant to section 505G of the FD&C Act (often referred to as *over-the-counter (OTC) monograph drugs*) and drugs compounded by outsourcing facilities pursuant to section 503B of the FD&C Act. The term also encompasses such drugs or biological products when they are included as a constituent part of a combination product, as defined in FDA regulations at 21 CFR 3.2(e).

<sup>3</sup> Some ophthalmic products that are the subject of this guidance may be combination products (see 21 CFR 3.2). See section VII for more information. Contact the Office of Combination Products at [Combination@fda.hhs.gov](mailto:Combination@fda.hhs.gov) with questions regarding the classification of a specific product.

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33 This guidance provides information regarding quality considerations for ophthalmic drug  
34 products consistent with the current good manufacturing practice (CGMP) requirements outlined  
35 in section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR  
36 parts 210 and 211 for all drug products, part 601 for biological products, and part 4 for  
37 combination products.<sup>4</sup> For ophthalmic drug products with a United States Pharmacopeia (USP)  
38 monograph, this guidance provides information about applicable criteria from the USP.<sup>5</sup> This  
39 guidance also provides recommendations to industry on the documentation that should be  
40 submitted in the chemistry, manufacturing, and controls (CMC) section of new drug applications  
41 (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications  
42 (BLAs), including BLAs for biosimilar and interchangeable biosimilar products.<sup>6</sup> The CMC  
43 section of NDAs, ANDAs, and BLAs must be included as required by 21 CFR 314.50, 21 CFR  
44 314.94, and 21 CFR part 601, respectively. Relevant records and other information that  
45 demonstrate compliance with CGMP requirements must be made available for FDA review  
46 during an inspection conducted under section 704(a)(1) of the FD&C Act or when requested by  
47 FDA in advance or in lieu of an inspection as described in section 704(a)(4) of the FD&C Act.<sup>7</sup>  
48 This guidance does not apply to biological products regulated by the Center for Biologics  
49 Evaluation and Research.

50  
51 This guidance revises the draft guidance of the same name issued in October 2023. This revision  
52 adds microbiological considerations related to product sterility for all ophthalmic drug products  
53 and the prevention of contamination of ophthalmic drug products packaged in multidose  
54 containers.

55  
56 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
57 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
58 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
59 the word *should* in Agency guidances means that something is suggested or recommended, but  
60 not required.

61  
62

## **II. MICROBIOLOGICAL CONSIDERATIONS**

63  
64

### **A. Product Sterility**

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66  
67  
68

Product sterility is a critical quality attribute (CQA) for ophthalmic drug products.<sup>8</sup> Recent cases  
of microbially contaminated ophthalmic drug products leading to serious injury and death, as

---

<sup>4</sup> In addition, applicants, manufacturers, and outsourcing facilities should ensure that drug products subject to this guidance comply with other applicable provisions of the FD&C Act, including sections 501(a)(2)(A), 501(a)(1), 501(c), 502(a), and 502(j).

<sup>5</sup> See section 501(b) of the FD&C Act.

<sup>6</sup> For topical ophthalmic biological products, including biosimilars and interchangeable products, we recommend that applicants consult with FDA before submitting their application.

<sup>7</sup> See also 21 CFR 211.180(c).

<sup>8</sup> See 21 CFR 200.50(a)(1).

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69 well as recent recalls, highlight the importance of product sterility.<sup>9</sup> Manufacturers<sup>10</sup> of sterile  
70 drug products must comply with CGMP requirements to ensure product sterility.<sup>11</sup> Failure to  
71 comply with these requirements will cause affected products to be deemed adulterated under  
72 section 501(a)(2)(B) of the FD&C Act.

73  
74 For recommendations on how to meet CGMP requirements for product sterility, see guidances  
75 for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good*  
76 *Manufacturing Practice* (September 2004) and *Submission Documentation for Sterilization*  
77 *Process Validation in Applications for Human and Veterinary Drug Products* (November  
78 1994).<sup>12</sup>

### 80 B. Multidose Drug Products

81  
82 Ophthalmic drug products should be appropriately designed and controlled to prevent harmful  
83 microbial contamination throughout their shelf life and in-use period, which must be supported  
84 by stability data.<sup>13</sup> Unit-dose CCSs prevent the hazards associated with in-use contamination and  
85 growth of microorganisms between doses that can occur with multidose CCSs that are opened  
86 multiple times over the course of their shelf life. Liquid ophthalmic drug products packaged in  
87 multidose containers should contain one or more suitable substances that will preserve the  
88 product and minimize the hazard of injury resulting from incidental contamination during use.<sup>14</sup>  
89 If a multidose drug product does not possess inherent antimicrobial activity adequate to preserve  
90 the formulation, it should be formulated with an appropriate preservative.<sup>15</sup> Preservatives are  
91 critical to ensuring that the multidose drug product remains free from harmful contamination  
92 following potential microbial ingress. Such ingress could occur, for example, if surrounding air  
93 is introduced into the multidose drug product following administration, if the tip of a dropper is  
94 contaminated by a nonsterile surface (i.e., the fluid path is contaminated), or if a contaminated  
95 drop returns to the product reservoir. Regardless of whether a multidose drug product possesses  
96 inherent antimicrobial activity or contains one or more added preservatives, manufacturers

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<sup>9</sup> See FDA's alerts and warnings about eye drops at <https://www.fda.gov/drugs/buying-using-medicine-safely/what-you-should-know-about-eye-drops>.

<sup>10</sup> For the purposes of this guidance, we use the term *manufacturer* to refer to entities that produce the drug products defined in footnote 2. Where applicable, this guidance uses the term *applicant* to refer to manufacturers and other parties who are NDA, ANDA, and BLA applicants or application holders.

<sup>11</sup> See, e.g., 21 CFR 211.22(a), 211.94(b), 211.113(b), 211.160, 211.165, 211.166, and 211.167.

<sup>12</sup> Although the latter guidance on sterilization process validation is intended for the submission of documentation for application products, its principles are also instructive for OTC monograph drugs. 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>.

<sup>13</sup> See 21 CFR 211.137 and 211.166.

<sup>14</sup> See 21 CFR 200.50(b)(1). If such substance(s) are not included in the drug product, other packaging and labeling recommendations apply. See 21 CFR 200.50(b)(2).

<sup>15</sup> For further discussion about the use of preservatives, see draft guidance for industry *Microbiological Quality Considerations in Non-Sterile Drug Manufacturing* (September 2021) at page 6. When final, this guidance will represent the FDA's current thinking on this topic.

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97 should implement a well-designed and rigorous antimicrobial effectiveness testing program that  
98 covers the product's shelf life.<sup>16</sup>  
99

100 FDA does not recommend using silver sulfate or other silver-containing compounds as a  
101 preservative in ophthalmic drug products because of the significant safety concerns associated  
102 with applying silver directly to the eye, including argyria (an irreversible discoloration of the  
103 skin and eyes) and granular deposits of silver in the conjunctiva and cornea.<sup>17</sup>  
104

105 Some manufacturers have sought to use a preservative-free formulation for a multidose liquid  
106 drug product in conjunction with a CCS design intended to eliminate the potential for in-use  
107 microbial contamination.<sup>18</sup> These formulations and associated presentations should afford robust  
108 protection for each unit produced to prevent the hazard of injury resulting from exposure to  
109 incidental contamination during multiple uses of the product.<sup>19</sup> There are numerous ways in  
110 which such presentations might fail to prevent microbial contamination. Any ophthalmic drug  
111 product that lacks adequate preservative properties, when exposed to in-use contamination, is  
112 especially vulnerable to proliferation of microbes that can pose severe harm to consumers. CCSs  
113 must provide adequate protection against foreseeable external factors in storage and use that can  
114 cause deterioration or contamination.<sup>20</sup>  
115

116 For information on delivery and dispensing characteristics of multidose containers, see section  
117 VII.B.2 of this guidance.  
118  
119

### **III. VISIBLE PARTICULATE MATTER**

120 The use of a robust visual inspection program and the implementation of CGMP requirements  
121 are important to ensure products are not adulterated. For topical ophthalmic drug products  
122 packaged in opaque containers, appropriate technologies (e.g., X-ray spectroscopy) or  
123 destructive testing should be used to identify particulates within the accepted visible size range.<sup>21</sup>  
124  
125  
126

127 Ophthalmic drug products with names recognized in the USP are generally required to also meet  
128 the particulate matter requirements in USP General Chapter <771> *Ophthalmic Products*—

---

<sup>16</sup> See USP General Chapter <51> *Antimicrobial Effectiveness Testing*.

<sup>17</sup> FDA also does not recommend using silver in CCSs for ophthalmic drug products because silver may continually leach into the drug product.

<sup>18</sup> Liquid ophthalmic preparations packed in multidose containers that do not contain one or more suitable and harmless substances that will inhibit the growth of microorganisms should be packaged and labeled with necessary warnings to minimize injury from contamination during use. See 21 CFR 200.50(b).

<sup>19</sup> *Ibid.* Furthermore, appropriate written procedures designed to prevent microbial contamination of sterile products must be established and followed, including validation of all aseptic and sterilization processes. See 21 CFR 211.113(b).

<sup>20</sup> See 21 CFR 211.94(b).

<sup>21</sup> For topical ophthalmic drug products that include inherent visible particulates by design, such as suspensions and emulsions, stability testing can be used to evaluate any changes in the particle size over the shelf life of the product. See USP General Chapter <771> *Ophthalmic Products—Quality Tests*.

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129 *Quality Tests*.<sup>22</sup> Noncompendial ophthalmic drug products should also follow the above USP  
130 General Chapter. Adherence to compendial standards can assist applicants and manufacturers in  
131 complying with CGMP regulations (e.g., 21 CFR 211.165(e), 211.167(b), and 211.194(a)(2)).  
132  
133

### **IV. EXTRACTABLES AND LEACHABLES**

136 Ophthalmic drug products should be evaluated for extractables and leachables from the CCS.  
137 Leachables have the potential to interact with the formulated drug product, which could  
138 compromise product quality and therapeutic effect. The assessment of extractables and  
139 leachables should consider the primary, secondary, and tertiary packaging components of the  
140 CCS, including the labeling components.  
141

142 Semipermeable CCSs can, over time, leach low molecular weight compounds (e.g., plasticizers,  
143 lubricants, pigments, stabilizers, antioxidants, binding agents) from CCS components or from  
144 labeling components (e.g., inks, adhesives, varnishes) into the drug product. However, this is less  
145 of a concern for products packaged in glass containers (e.g., biological products).  
146

147 General tests for CCSs are described in USP General Chapters, such as <87> *Biological*  
148 *Reactivity Tests, In Vitro*; <88> *Biological Reactivity Tests, In Vivo*; <660> *Containers—Glass*;  
149 and <661> *Plastic Packaging Systems and Their Materials of Construction*. For more  
150 information about testing extractables and leachables, applicants and manufacturers should  
151 consult USP General Chapters <1663> *Assessment of Extractables Associated With*  
152 *Pharmaceutical Packaging/Delivery Systems* and <1664> *Assessment of Drug Product*  
153 *Leachables Associated With Pharmaceutical Packaging/Delivery Systems*. Applicants should  
154 also refer to the guidance for industry *Container Closure Systems for Packaging Human Drugs*  
155 *and Biologics: Chemistry, Manufacturing, and Controls Documentation* (May 1999).  
156

#### **A. Extractables Studies**

157  
158  
159 Where extractables testing is conducted to comply with CGMP requirements, manufacturers  
160 should document the following information about their extractables studies, and applicants  
161 should provide this information in their application (see 21 CFR 211.194(a)).  
162

- 163 • A risk assessment in support of their study approach.
- 164
- 165 • Data from their extractables studies, which generally should be conducted following the  
166 framework provided in USP General Chapter <1663> and should take into account the  
167 primary, secondary, and tertiary packaging components.
- 168
- 169 • Information on the use of extraction conditions (e.g., media, temperature, time, analytical  
170 techniques).  
171

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<sup>22</sup> See section 501(b) of the FD&C Act.

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- 172       • Information on the use of analytical procedures (e.g., gas or liquid chromatography–mass  
173       spectrometry), including method validation information.  
174  
175       • An assessment of the resultant extractables profiles.  
176

177       Where a CCS has been used in an approved ophthalmic drug product, an applicant can refer to  
178       previously submitted information to address the recommendations above, when feasible and with  
179       adequate justification.

180

### **B. Leachables Studies**

182

183       Because leachables can stem from different sources and be formulation dependent, applicants  
184       and manufacturers should have adequate data to identify and characterize the potential risks  
185       associated with the leachables from the CCS and describe how these risks are mitigated, such as  
186       by conducting leachables studies.

187

188       Where leachables testing is conducted to comply with CGMP requirements, manufacturers  
189       should document the following information about their leachables studies, and applicants should  
190       provide this information in their application (see 21 CFR 211.194(a)).

191

- 192       • Data from three primary stability batches, each of which generally should be followed  
193       through expiry as described in USP General Chapter <1664>.  
194  
195       • Information on the use of analytical procedures (e.g., gas or liquid chromatography–mass  
196       spectrometry), including method validation information.  
197  
198       • An assessment of the resultant leachables profiles.<sup>23</sup>  
199  
200       • The acceptance criteria contained in drug product specifications.<sup>24</sup>

201

202       In addition to the leachables studies, a separate toxicological risk assessment of the leachables  
203       should be conducted.

204

### **C. Safety Thresholds**

206

207       Because of the variety of chemical species and the enormous capability of modern analytical  
208       techniques in detecting trace amounts of chemicals, it is neither practical nor necessary to  
209       identify all detected leachables for safety qualification. However, because ophthalmic drug  
210       products are applied directly to the eye, applicants and manufacturers should assess compatibility  
211       and safety concerns of any potential leachables exceeding the qualification threshold discussed  
212       below. The safety assessment should address the ocular toxicity and irritancy potential of such  
213       leachables, in addition to systemic safety, as appropriate.

214

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<sup>23</sup> See section IV.C of this guidance.

<sup>24</sup> Ibid.

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215 Applicants and manufacturers can use a safety threshold approach to assess the potential of  
216 leachables and extractables to leach into and/or interact with the formulated drug product. The  
217 following recommended leachables thresholds are expressed in parts per million (ppm) (i.e., the  
218 parts of a leachable per unit mass of the ophthalmic drug product)<sup>25</sup>:

219

- 220 • Reporting threshold: 1 ppm.
- 221 • Identification threshold: 10 ppm.
- 222 • Qualification threshold: 20 ppm.

223

224 Manufacturers should document information about their safety thresholds, and applicants should  
225 list leachable impurities above the reporting threshold along with other impurities in the drug  
226 product specification section of NDAs and ANDAs, but not in BLAs (see 21 CFR 211.194).<sup>26</sup>

227

228

### **V. IMPURITIES AND DEGRADATION PRODUCTS**

229

230

231

#### **A. NDA, ANDA, and OTC Monograph Drugs**

232

233 The establishment of scientifically sound and appropriate specifications to comply with 21 CFR  
234 211.160(b) includes identifying test methods and acceptance criteria for impurities and  
235 degradation products. NDA and ANDA applicants should generally follow the principles of  
236 reporting, identifying, and qualifying degradation products and impurities outlined in the  
237 International Council for Harmonisation (ICH) guidance for industry *Q3B(R2) Impurities in New*  
238 *Drug Products* (August 2006).<sup>27</sup> Manufacturers should generally establish thresholds and  
239 acceptance criteria for impurities and degradation products according to USP General Chapter  
240 <1086> *Impurities in Drug Substances and Drug Products*. Manufacturers should document the  
241 following information and applicants should include it in the drug product specification section  
242 of NDAs or ANDAs (21 CFR 211.194(a)):

243

- 244 • Each specified identified degradation product or impurity as a percentage of the active  
245 pharmaceutical ingredient (API).
- 246
- 247 • Each specified unidentified degradation product or impurity as a percentage of the API.
- 248
- 249 • Any individual unspecified degradation product or impurity.
- 250
- 251 • Total degradation products or impurities.

252

253 However, FDA's recommended thresholds for individual unspecified degradation products or  
254 impurities are different for ophthalmic drug products than the corresponding thresholds provided

---

<sup>25</sup> These thresholds are based on historical data from approved drug products. For topical ophthalmic drug products, ppm is used instead of a limit on concentration because of the risk of local toxicity to the eye.

<sup>26</sup> See section V.B of this guidance for an explanation of this recommendation for BLAs.

<sup>27</sup> Acceptance criteria for specified degradation products in generic drug products should be established according to the guidance for industry *ANDAs: Impurities in Drug Products* (November 2010).

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255 in ICH Q3B(R2) for the same dose range (see table below for these different thresholds, which  
256 are based on historical data from FDA-approved drug products). There are two reasons for the  
257 differences in recommended thresholds compared to the ICH recommendations: First,  
258 ophthalmic drug products are directly administered to the eye, and direct, local application has  
259 the potential to produce high local concentrations in the eye. In contrast, the recommendations in  
260 ICH Q3B(R2) are generally used to support safety determinations for drug products that act  
261 systemically. Second, these differences also account for the fact that less is known about the  
262 potential effects of individual unspecified degradation products or impurities than specified  
263 degradation products or impurities.

### 265 FDA's Recommended Thresholds for Unspecified Degradation Products or Impurities 266 in Ophthalmic Drug Products\*

Drug Product Strength (% w/v)	Recommended Identification and Qualification Threshold
Greater than 0.1% to less than or equal to 1%** ( $> 0.1\%$ to $\leq 1\%$ )	0.1%
Less than or equal to 0.1% ( $\leq 0.1\%$ )	1% or 1 ppm***

267 \*These recommended thresholds apply to OTC monograph ophthalmic drug products and ophthalmic drug  
268 products submitted under NDAs and ANDAs.

269 \*\* Limits above 1% will be evaluated on a case-by-case basis.

270 \*\*\* Whichever is higher; ppm=parts per million (i.e., parts of a leachable per unit mass of the ophthalmic  
271 drug product).

272  
273 For individual unspecified degradation product or impurity limits that exceed the recommended  
274 thresholds in the table above, manufacturers should document identification and safety  
275 information for the degradation product or impurity, and applicants should provide such  
276 information in their application. Safety information should address both local ocular toxicity as  
277 well as general systemic toxicity.

### 278 279 **B. BLAs**

280  
281 For ophthalmic biological products, degradation products or product impurities can be controlled  
282 by specific acceptance criteria at release and under storage based on historical ranges in pivotal  
283 clinical trials. However, some ophthalmic biological products include product-related substances  
284 (including some that form under storage) that retain biological activity. Moreover, individual  
285 quantitation of each of these individual species may not always be technically feasible. For this  
286 reason, impurity considerations for ophthalmic biological products should include product-  
287 related substances in addition to degradation products and product-related impurities. Therefore,  
288 for ophthalmic biological products, specifications should be established for attributes (e.g.,  
289 charge variant profile) that are known to be reflective of the mixture of product-related  
290 substances and product-related impurities. Other impurities, such as process impurities, can be  
291 controlled by using (1) drug product release criteria based on risk assessments for each impurity  
292 or impurity class (i.e., host cell proteins), and (2) historical process clearance. Applicants should  
293 establish acceptance criteria for impurities, including leachables and process impurities, as

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294 required to control product quality, safety, and efficacy.<sup>28</sup> Impurity amounts should be clearly  
295 defined as a percentage of the active ingredient or in current conventional units for ophthalmic  
296 biological products (e.g., milligram/milliliter (mg/mL), microgram/milliliter (µg/mL),  
297 nanogram/milligram (ng/mg)).  
298  
299

### **VI. IN VITRO DRUG RELEASE/DISSOLUTION TESTING FOR QUALITY CONTROL**

303 The rate and extent of drug release from ophthalmic drug products are quality criteria that may  
304 reflect aspects related to formulation and process variants that are important to control to ensure  
305 consistent quality. One approach that applicants can consider as part of the quality control  
306 strategy for certain ophthalmic dosage forms (e.g., suspensions, emulsions, semi-solids) is the  
307 use of in vitro drug release/dissolution testing. Other approaches are also acceptable, such as  
308 using one or more CQAs that are sensitive to the formulation and process variants. The applicant  
309 should provide scientific justification for how the control strategy will ensure consistent product  
310 quality.  
311

### **VII. CCS DESIGN AND DELIVERY AND DISPENSING CHARACTERISTICS**

315 This section describes recommendations regarding design elements and delivery and dispensing  
316 characteristics that applicants and manufacturers should consider for ophthalmic drug product  
317 CCSs. When the CCS that holds or contains an ophthalmic drug also delivers it, it may also be a  
318 device constituent part and, together with the drug contained within, a combination product (see  
319 21 CFR 3.2(e)). Combination products are subject to the CGMP requirements under 21 CFR part  
320 4, subpart A.<sup>29</sup>  
321

#### **A. CCS Design**

##### *1. Tamper-Evident Packaging*

326 All containers of ophthalmic drug products must be sterile at the time of filling and closing and  
327 sealed to prevent product use without destruction of the seal.<sup>30</sup> Additionally, ophthalmic drug  
328 products that are OTC drugs must comply with the tamper-evident packaging requirements of 21  
329 CFR 211.132. If the CCS has a nonretaining tamper-evident ring (e.g., collar or band) to seal the  
330 bottle and cap, special care should be taken so that the ring does not detach from the bottle  
331 during use, which could cause an eye injury. OTC drugs with tamper-evident rings should also

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<sup>28</sup> See ICH guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999).

<sup>29</sup> For further information, see the guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017). See also the guidance for industry *Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4* (March 2022) for more information regarding ophthalmic drugs and biological products packaged with eye cups, eye droppers, or other dispensers.

<sup>30</sup> See 21 CFR 200.50(a)(3).

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332 include a positive-retention mechanism similar to those on disposable plastic beverage bottles to  
333 prevent the rings from coming off during use.

334

### 335 2. *Tips*

336

337 For CCS designs in which the tip is sealed until opening, multistep procedures are discouraged  
338 because a patient may touch and contaminate the tip with their hands while attempting to unseal  
339 it. FDA recommends use of single-step procedures that involve simple directions and twisting  
340 the cap without removing it.

341

### 342 3. *Torque Specifications*

343

344 Applicants and manufacturers should consider the torque specifications for drug product CCSs  
345 because some patients may have difficulties twisting off CCS caps that require extra effort to  
346 open. FDA recommends that torque be low enough so that special populations, including the  
347 elderly, can open caps without undue difficulty but high enough so that caps remain in place  
348 during manufacturing, storage, shipping, and handling.

349

### 350 4. *Color Coding*

351

352 Color coding the caps of ophthalmic drug products is an effective tool in characterizing their  
353 therapeutic class.<sup>31</sup> FDA recommends that applicants and manufacturers use a uniform color-  
354 coding system as described in the American Academy of Ophthalmology's *Color Codes for*  
355 *Topical Ocular Medications* policy statement.<sup>32</sup>

356

## 357 **B. Delivery and Dispensing Characteristics**

358

### 359 1. *Unit Dose Containers*

360

361 For all topical ophthalmic drug products,<sup>33</sup> FDA recommends that the maximum fill volume of a  
362 unit dose (nonpreserved) container be no more than 0.5 mL for solutions, emulsions, and  
363 suspensions. FDA also recommends that the maximum fill for a unit dose ointment or gel be no  
364 more than 1 gram. Unit dose containers should not be able to be recapped.

365

### 366 2. *Multidose Containers*

367

#### 368 a. Drop size

369

370 For all topical ophthalmic drug products,<sup>34</sup> FDA recommends that the drop size in a multidose  
371 CCS be between 20 and 70 microliters.

---

<sup>31</sup> See guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022).

<sup>32</sup> See <https://www.aaopt.org/about/policies/color-codes-topical-ocular-medications>.

<sup>33</sup> See footnote 2.

<sup>34</sup> *Ibid.*

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*Draft — Not for Implementation*

372  
373 For ophthalmic drug products submitted for approval under an ANDA, applicants should  
374 conduct a one-time drop volume/drop weight study to determine drop size during delivery or  
375 dispensing. The drop size of the generic product should be within  $\pm 10\%$  of the drop size for the  
376 reference listed drug (RLD) and within the recommended drop size of 20 to 70 microliters. For  
377 any deviations from the RLD, the ANDA applicant should provide a justification to demonstrate  
378 that there will be a similar number of delivered doses as the RLD. ANDA submissions should  
379 include information on the measurement of drop volume/drop weight and testing conditions,  
380 such as the number of drops in the container and its holding angle during dosing.

### b. Dose uniformity of suspension drug products

381  
382  
383 As recommended in USP General Chapter <771> *Ophthalmic Products—Quality Tests*, a  
384 resuspendability/redispersibility test should be performed for all ophthalmic suspension drug  
385 products. For multidose containers, data for a one-time dose-uniformity study (from top, middle,  
386 and bottom of the container) should be provided from at least three pilot or exhibit batches to  
387 demonstrate that the drug substance is uniformly dispersed and the labeled dose can be  
388 consistently delivered throughout the shelf life. Alternatively, applicants may consider providing  
389 data from development batches (such as investigational new drug batches) that represent the to-  
390 be-marketed formulation to demonstrate dose uniformity.

391

392

393

## **VIII. STABILITY**

394

395

396 Manufacturers of drug products must establish a program to evaluate the stability of drug  
397 products and to use the results of the stability testing to determine appropriate storage conditions  
398 and expiration dates (21 CFR 211.166). The following stability recommendations should be  
399 considered when developing a stability testing program.<sup>35</sup>

400

### **A. Container Orientation During Storage**

401

402

403 The stability of ophthalmic drug products can be affected when they are stored under different  
404 orientations. Before conducting primary stability studies, NDA applicants should conduct  
405 preliminary development work<sup>36</sup> to evaluate storage conditions in two different orientations—an  
406 upright position and either an inverted or horizontal position. Data from this preliminary work  
407 should be used to capture and characterize differences in quality attributes, if any, and determine  
408 the worst-case orientation. NDA applicants should use this worst-case orientation when  
409 conducting stability tests using batches that represent the commercial manufacturing process.

410

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<sup>35</sup> For detailed information on the stability protocol, annual stability testing, and data reporting, refer to the FDA guidances for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003); *ANDAs: Stability Testing of Drug Substances and Products* (June 2013) and *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers* (May 2014). For BLA products, refer to the ICH guidance for industry *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (July 1996).

<sup>36</sup> See guidance for industry *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information* (May 2003).

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*Draft — Not for Implementation*

411 Products submitted under a BLA do not rely on preliminary development work to establish  
412 storage conditions during stability. Rather, these products rely on primary stability studies,  
413 frequently including process validation batches, to determine storage under real-time conditions.  
414 Where interactions between a formulated liquid biological product and the CCS (other than  
415 sealed ampules) cannot be excluded, applicants should place stability samples in an upright  
416 position and in either an inverted or horizontal position (i.e., in contact with all CCS surfaces) to  
417 determine the effect of all product-contact CCS components on product quality.<sup>37</sup>  
418

419 For products submitted for approval under an ANDA, applicants should place primary stability  
420 batches in an upright position and either an inverted or horizontal position, and data from both  
421 orientations should be provided in the original submission. The determination of worst-case  
422 orientation from this comparison should be used to justify use of that orientation for routine  
423 stability batches following approval.<sup>38</sup>  
424

425 Manufacturers must have a written stability testing program that includes the storage conditions  
426 for samples retained for testing (see 21 CFR 211.166(a)(2)), and should generally follow similar  
427 principles to determine the worst-case orientation for stability studies.  
428

### **B. Water Loss**

429  
430  
431 For ophthalmic drug products packaged in semipermeable CCSs, applicants and manufacturers  
432 should conduct a water loss test to assess the moisture transmission properties of the CCS and the  
433 protective properties of any secondary packaging used. Where water loss testing is conducted to  
434 comply with CGMP requirements, manufacturers should document information on the test  
435 methods and acceptance criteria used, and applicants should include such information in their  
436 application (see 21 CFR 211.194(a)).  
437

### **C. Freeze/Thaw Study for Emulsions and Suspensions**

438  
439  
440 For ophthalmic drug products that are emulsions or suspensions, applicants and manufacturers  
441 should perform a one-time freeze/thaw thermal cycling study to evaluate the effects of any high  
442 and low temperature variations that may be encountered during shipping and handling, which  
443 could affect the quality and performance of the drug product.<sup>39</sup> FDA recommends this study  
444 consist of three cycles, with temperatures cycling between freezing (-20 °C to 0 °C) and ambient  
445 (25 °C to 35 °C) temperatures for a cumulative minimum of 3 days. Periodically throughout the  
446 study, and at the end of a predetermined number of cycles, the samples should be analyzed for all  
447 quality attributes and compared with the control drug product. Applicants that use alternative  
448 conditions and durations for their tests should provide a justification for the test conditions used.  
449

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<sup>37</sup> See ICH guidance for industry *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (July 1996).

<sup>38</sup> See guidance for industry *ANDAs: Stability Testing of Drug Substances and Products Questions and Answers* (May 2014).

<sup>39</sup> See guidance for industry *Drug Stability Guidelines* (December 2008). This guidance was published by the Center for Veterinary Medicine, but FDA recommends that its thermal cycling study recommendations also be applied to drugs intended for human use.

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### 450 D. In-Use Stability Studies

451  
452 In-use stability studies are used to determine expiration dates and support labeling claims for  
453 appropriate storage conditions that may change after opening, such as a change in temperature or  
454 light exposure (see 21 CFR 211.166, 21 CFR 211.137(b)). Manufacturers should document  
455 information on in-use stability studies, and applicants should submit such information in their  
456 application.

457  
458 Under 21 CFR 211.137(h), OTC drugs that do not bear dosage limitations in their labeling and  
459 are stable for at least 3 years, as supported by appropriate stability data, are exempt from the  
460 expiration date labeling requirement. Accelerated testing programs can be appropriate to  
461 establish stability for the purposes of meeting this requirement.

462  
463

### 464 IX. GLOSSARY

465  
466 **Container closure system (CCS):** For the purpose of this guidance, the CCS includes primary  
467 packaging components (e.g., bottles, drug-dispensing tips, tubes with liner, caps), secondary  
468 packaging components (e.g., overwrap), and tertiary packaging components (e.g., shipping  
469 boxes).

470  
471 **Critical quality attribute:** “Physical, chemical, biological, or microbiological property or  
472 characteristic that should be within an appropriate limit, range, or distribution to ensure the  
473 desired product quality.”<sup>40</sup>

474  
475 **Degradation product:** “An impurity resulting from a chemical change in the drug substance  
476 brought about during manufacture and/or storage of the new drug product by the effect of, for  
477 example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate  
478 container closure system.”<sup>41</sup>

479  
480 **Extractables:** “Organic and inorganic chemical entities that are released from a pharmaceutical  
481 packaging/delivery system, packaging component, or packaging material of construction and into  
482 an extraction solvent under laboratory conditions.”<sup>42</sup>

483  
484 **Impurity:** “Any component of the new drug product that is not the drug substance or an  
485 excipient in the drug product.”<sup>43</sup>

486  
487 **Leachables:** “Foreign organic and inorganic chemical entities that are present in a packaged  
488 drug product because they have leached into the packaged drug product from a  
489 packaging/delivery system, packaging component, or packaging material of construction under

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<sup>40</sup> ICH guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

<sup>41</sup> ICH Q3B(R2).

<sup>42</sup> USP General Chapter <1663>.

<sup>43</sup> ICH Q3B(R2).

## *Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

490 normal conditions of storage and use or during accelerated drug product stability studies.”<sup>44</sup>

491

492 **Preservative:** A substance added to a drug product to protect it from the growth of  
493 microorganisms.

494

495 **Semipermeable CCS:** CCSs that permit the passage of solvent or foreign volatile materials  
496 through the CCS wall.

497

498 **Specified degradation product:** “A degradation product that is individually listed and limited  
499 with a specific acceptance criterion in the new drug product specification. A specified  
500 degradation product can either be identified or unidentified.”<sup>45</sup>

501

502 **Specified impurity:** An impurity that is individually listed and limited with a specific  
503 acceptance criterion in the new drug substance specification. A specified impurity can be either  
504 identified or unidentified.

505

506 **Unidentified degradation product:** “A degradation product for which a structural  
507 characterization has not been achieved and that is defined solely by qualitative analytical  
508 properties (e.g., chromatographic retention time).”<sup>46</sup>

509

510 **Unidentified impurity:** An impurity for which a structural characterization has not been  
511 achieved and is defined solely by qualitative analytical properties (e.g., chromatographic  
512 retention time).

513

514 **Unspecified degradation product:** “A degradation product that is limited by a general  
515 acceptance criterion, but not individually listed with its own specific acceptance criterion, in the  
516 new drug product specification.”<sup>47</sup>

517

518 **Unspecified impurity:** An impurity that is limited by a general acceptance criterion but not  
519 listed with its own specific acceptance criterion in the new drug substance specification.

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<sup>44</sup> USP General Chapter <1664>.

<sup>45</sup> ICH Q3B(R2).

<sup>46</sup> Ibid.

<sup>47</sup> Ibid.