
Sameness Evaluations in an ANDA — Active Ingredients Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. 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. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Susan Levine 240-402-7936.

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

**November 2022
Generic Drugs**

Sameness Evaluations in an ANDA — Active Ingredients 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>*

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

**November 2022
Generic Drugs**

Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	BACKGROUND	1
III.	ACTIVE INGREDIENT SAMENESS EVALUATIONS	3
A.	General Considerations for Determining the Active Ingredient	4
B.	Active Ingredient Sameness Considerations in Certain Drug Products	5
1.	<i>Synthetic Peptides</i>	<i>5</i>
2.	<i>Complex Mixtures</i>	<i>6</i>
C.	Characterization of the Active Ingredient in the Drug Product	7
D.	Additional Recommendations	9

Contains Nonbinding Recommendations

Draft — Not for Implementation

**Sameness Evaluations in an ANDA — Active Ingredients
Guidance for Industry¹**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist applicants preparing an abbreviated new drug application (ANDA) by providing recommendations on demonstrating sameness² between the active ingredient in a proposed generic drug product³ and its reference listed drug (RLD)⁴ as required under section 505(j)(2)(A)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)(2)(A)(ii)) and FDA’s regulations in § 314.94(a)(5) (21 CFR 314.94(a)(5)).

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and 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.

II. BACKGROUND

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (Hatch-Waxman Amendments) created an approval pathway for generic drug products under which applicants can submit an ANDA under section 505(j) of the FD&C Act. An ANDA relies on the Agency’s previous finding of safety and effectiveness for an RLD and, as a result, may be

¹ This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research at FDA.

² For purposes of this guidance, the term *sameness* is used to describe the requirement that a drug product proposed in an ANDA have the same active ingredient as the drug product it references. See section II of this guidance for more information.

³ § 314.3(b) (21 CFR 314.3(b)). A *drug product* is “a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.”

⁴ § 314.3(b). A *reference listed drug* is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.

Contains Nonbinding Recommendations

Draft — Not for Implementation

35 approved without submission of the same type and extent of information that is required for
36 approval of a new drug application (NDA) submitted under section 505(b) of the FD&C Act.⁵
37

38 Among other things, an ANDA must contain information to show that the active ingredient of
39 the proposed generic drug product is the “same as” that of the RLD.^{6,7,8} FDA’s regulations
40 provide that the term “same as” means, among other things, “identical in active ingredient(s).”⁹
41 *Active ingredient* is defined as:

42
43 [A]ny component that is intended to furnish pharmacological activity or other direct
44 effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect
45 the structure or any function of the body of man or other animals. The term includes
46 those components that may undergo chemical change in the manufacture of the drug
47 product and be present in the drug product in a modified form intended to furnish the
48 specified activity or effect.^{10,11}
49

50 The preamble of the proposed rule implementing the Hatch-Waxman Amendments states that
51 “[a]ctive ingredient in this context means the active ingredient in the finished drug product prior
52 to its administration.”¹² FDA recommends that applicants evaluate active ingredient sameness
53 using the active ingredient as it exists in the drug product (i.e., in the finished dosage form).¹³
54 Accordingly, applicants should fully evaluate the potential for changes in or to the active
55 ingredient during the manufacturing process of the drug product.
56

⁵ Compare section 505(j)(2)(A) of the FD&C Act with section 505(b) of the FD&C Act.

⁶ § 314.94(a)(5).

⁷ If the active ingredient in an applicant’s proposed generic drug product cannot be demonstrated to be the same as the active ingredient in the RLD by using the information and data that may be submitted in an ANDA, the proposed drug product should not be submitted for approval in an ANDA. See section 505(j)(2)(A)(ii) and 505(j)(4)(C) of the FD&C Act; see also the guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019), at page 8. 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>.

⁸ An applicant may submit a suitability petition to FDA requesting permission to submit an ANDA for a proposed generic drug product that differs from an RLD in that it has one different active ingredient in a fixed-combination drug product. See section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93.

⁹ 21 CFR 314.92(a)(1). The regulation states in part that “[f]or determining the suitability of an abbreviated new drug application, the term ‘same as’ means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted.”

¹⁰ § 314.3(b).

¹¹ This guidance uses the term “active ingredient”, as defined in the regulations (21 CFR 314.3(b)), which pertains to both human and animal drugs, and components that may undergo a chemical change during manufacturing and be present in a modified form intended to furnish the specified activity or effect.

¹² 54 FR 28872 at 28881 (July 10, 1989).

¹³ See footnote 3.

Contains Nonbinding Recommendations

Draft — Not for Implementation

57 FDA will refuse to approve an ANDA if the ANDA contains insufficient information to show
58 that, among other things, the active ingredient of the proposed generic drug product is the same
59 as that of the RLD.¹⁴ Accordingly, the ANDA applicant is responsible for providing sufficient
60 information to demonstrate that the proposed generic drug product is the “same as” the RLD
61 with respect to the active ingredient. For fixed-combination drug products, i.e., drug products
62 with more than one active ingredient, the recommendations in this guidance apply to each active
63 ingredient.

64

65

III. ACTIVE INGREDIENT SAMENESS EVALUATIONS

66

67
68 FDA has broad discretion to determine whether an ANDA applicant has submitted information
69 sufficient for the Agency to reasonably conclude that the proposed generic drug product’s active
70 ingredient is the same as the active ingredient of the RLD.¹⁵ The statutory provisions outlining
71 the contents of an ANDA do not describe the type or amount of information that an ANDA
72 applicant must submit to demonstrate sameness. In the preamble to the final rule that
73 implemented the Hatch-Waxman Amendments (1992 Final Rule), FDA specifically declined to
74 require that applicants show active ingredient sameness by demonstrating that their active
75 ingredients “exhibit the same physical and chemical characteristics [as the RLD’s], that no
76 additional residues or impurities can result from the different manufacture or synthesis process;
77 and that the stereochemistry characteristics and solid state forms of the drug have not been
78 altered.”¹⁶ Instead, FDA adopted a more flexible approach in assessing whether a proposed
79 generic drug product contains the same active ingredient as that of the RLD.¹⁷

80

81 The preamble to the 1992 Final Rule indicated that “FDA will consider an active ingredient to be
82 the same as that of the RLD if it meets the same standards for identity. In most cases, these
83 standards are described in the U.S. Pharmacopeia [(USP)].”¹⁸ If there is no USP identity
84 standard for an active ingredient in an official monograph, FDA recommends an applicant
85 establish the identity of the active ingredient by using appropriate analytical methods (e.g., high-
86 performance liquid chromatography, titration, etc.). In other cases, “FDA may prescribe
87 additional standards that are material to the ingredient’s sameness.”¹⁹ FDA’s determination of
88 active ingredient sameness is based on relevant scientific information and is made as to the
89 individual active ingredient(s) presented in the proposed drug product.

90

¹⁴ 21 CFR 314.127(a)(3).

¹⁵ See generally *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998).

¹⁶ 57 FR 17950 at 17958-17959 (April 28, 1992).

¹⁷ *Id.* at 17959; see also letter from Janet Woodcock to J. Michael Nicholas (April 16, 2015), Docket No. FDA-2015-P-1050, at page 7 (denying citizen petition from Teva Pharmaceuticals).

¹⁸ 57 FR 17950 at 17959.

¹⁹ *Id.*

Contains Nonbinding Recommendations

Draft — Not for Implementation

91 Section III.B. of this guidance discusses how FDA generally intends to evaluate the sameness of
92 the active ingredient in certain proposed generic drug products compared to the active ingredient
93 in the RLD.

94

95 A. General Considerations for Determining the Active Ingredient

96

97 *To assist prospective applicants in evaluating and demonstrating sameness, this section provides*
98 *general information on active ingredient sameness issues that FDA generally intends to*
99 *consider.*

100

101 This guidance provides recommendations on establishing the identity of an active ingredient to
102 demonstrate active ingredient sameness. As part of the identity of an active ingredient, we
103 generally consider the chemical form of an active ingredient to be the entire molecule, including
104 those portions of the molecule that cause the drug to be an ester or salt. For the evaluation of
105 sameness, the identity of the active ingredient may also encompass noncovalent derivatives (such
106 as a complex, chelate, or clathrate, with some limitations described below) of the molecule as it
107 exists in the drug product (i.e., in the finished dosage form²⁰). Instances where a complex,
108 clathrate, or chelate of an active ingredient may or may not be part of the chemical form of the
109 active ingredient are discussed in section III.C.

110

111 The same active ingredient can exist in more than one *physical form*, such as polymorphs²¹ or
112 co-crystals.^{22,23} Polymorphs are different crystalline forms of the same active ingredient; they
113 differ in internal solid-state structure but not in chemical structure. This may include solvate or
114 hydrate forms (also known as pseudopolymorphs) and amorphous forms. Co-crystals are
115 crystalline materials composed of two or more different molecules—the active ingredient and co-
116 crystal formers (coformers)—in a defined stoichiometric ratio within the same crystal lattice that
117 are associated by nonionic and noncovalent bonds. Co-crystals may be viewed as a special case
118 of solvates and hydrates, wherein the coformer is not a solvent (including water) and is typically
119 nonvolatile. In general, differences in physical form will not prevent a prospective ANDA

²⁰ See § 314.3(b) (definition of *drug product*).

²¹ See the guidance for industry *ANDAs: Pharmaceutical Solid Polymorphism: Chemistry, Manufacturing, and Controls Information* (July 2007) (Polymorph Guidance).

²² See the guidance for industry *Regulatory Classification of Pharmaceutical Co-Crystals* (February 2018) (Co-Crystals Guidance).

²³ We note that the Polymorph Guidance uses the terms *drug substance* and *active ingredient* interchangeably (Polymorph Guidance at page 1, footnote 4) and that the Co-Crystals Guidance uses the term *active pharmaceutical ingredient* in place of active ingredient. Though this guidance does distinguish between active ingredient and active pharmaceutical ingredient, the concepts articulated in the Polymorph Guidance and the Co-Crystal Guidance apply to the discussion here on *active ingredient*, as defined and used throughout this document.

Contains Nonbinding Recommendations

Draft — Not for Implementation

120 applicant from demonstrating active ingredient sameness between the active ingredient in the
121 ANDA drug product and the RLD.²⁴

122

B. Active Ingredient Sameness Considerations in Certain Drug Products

124

*1. Synthetic Peptides*²⁵

126

127 In general, FDA considers any amino acid polymer composed of 40 or fewer amino acids to be a
128 peptide regulated under the FD&C Act, rather than a protein regulated under the Public Health
129 Service Act.²⁶ Currently, FDA generally considers appropriate for submission in an ANDA
130 certain highly purified synthetic peptides that reference a previously approved synthetic peptide
131 drug product or a peptide of rDNA origin.²⁷ The sameness of the active ingredient of a proposed
132 generic synthetic peptide drug product (proposed generic synthetic peptide) can generally be
133 established through physicochemical characterization and biological evaluation.²⁸ Although
134 compendial standards may be available for some peptides for which an ANDA may be
135 appropriate, it is recommended that applicants also perform comparative testing of the proposed
136 generic synthetic peptide to the RLD.²⁹ For example, FDA recommends that ANDA applicants
137 apply orthogonal analytical methods to characterize the following properties:

138

- 139 • Primary sequence and physicochemical properties
- 140 • Secondary structure
- 141 • Oligomer/aggregation states
- 142 • Biological activities (by in vitro or animal studies)³⁰

²⁴ Polymorph Guidance at 6 (noting that over the years FDA has approved a number of ANDAs in which the active ingredient in the generic drug product had a different polymorphic form from the RLD (e.g., warfarin sodium, famotidine, and ranitidine), and that FDA also has approved some ANDAs in which the active ingredient in the generic drug product differed in solvate or hydrate forms from the RLD (e.g., terazosin hydrochloride, ampicillin, and cefadroxil)).

²⁵ See the guidance for industry *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin* (May 2021) (Peptides Guidance).

²⁶ See, e.g., 21 CFR 600.3(h)(6) (defining *protein*) and 85 FR 10057 (Feb. 21, 2020) (discussing FDA's interpretation of the term *protein*).

²⁷ See generally Peptides Guidance.

²⁸ Id. Irrespective of establishing the sameness of the active ingredient, “in some circumstances, peptide-related impurities may create the potential for differences in immunogenicity or may otherwise affect the safety or effectiveness of a peptide drug product.” Id. at 3. Thus, “the type of application that should be submitted for a proposed synthetic peptide that refers to a peptide of rDNA origin depends largely on the type of data that would be necessary to evaluate the difference in impurities between the proposed product and the previously approved product.” Id.

²⁹ See generally Peptides Guidance.

Contains Nonbinding Recommendations

Draft — Not for Implementation

143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173

2. Complex Mixtures

For an active ingredient in a complex mixture, FDA evaluates all relevant data in the ANDA and other relevant scientific information to determine whether an active ingredient of a complex mixture has been adequately characterized for the purposes of assessing active ingredient sameness. FDA recommends orthogonal methods to characterize components of the complex mixture and will consider the totality of evidence submitted to characterize the complex mixture.

In the past, FDA has identified several different categories of complex mixtures, for example: (1) naturally derived mixtures with multiple components (e.g., fish oil, conjugated estrogens); (2) synthetic *polymers* (e.g., sevelamer, colesevelam); and (3) synthetic or semi-synthetic mixtures (e.g., pentosan polysulfate, low-molecular weight heparins). In most instances, complex mixtures are treated as a single active ingredient because it is not possible to distinguish each and every specific constituent component in the complex mixture that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals.³¹ For certain complex mixtures, however, it may be possible to identify each and every constituent component in the mixture that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. For such complex mixtures, if there is more than one such constituent component identified in the complex mixture, FDA generally will treat each constituent component as a separate active ingredient. At the same time, FDA will generally not consider such mixtures to be fixed-combination drug products, since fixed-combination drug products contain separate active ingredients that have been intentionally combined together.³²

To support an active ingredient sameness determination for complex mixtures, we recommend that ANDA applicants characterize constituent components of the active ingredient in multiple batches of both the proposed generic drug product (test product) and reference product under similar conditions. In addition, to the extent a complex mixture contains well-characterized

³⁰ Id. We support the principle of principles of the “3Rs,” to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

³¹ For example, Conjugated Estrogens is treated as a single active ingredient. Conjugated Estrogens active pharmaceutical ingredient is obtained from a natural source and contains a mixture of many steroidal and nonsteroidal components derived from pregnant mares’ urine. Although it is not possible to distinguish each and every specific constituent component in the complex mixture that is intended to furnish pharmacological activity (or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals), the Conjugated Estrogens USP monograph defines 10 representative individual steroidal components and the acceptable criteria in the labeled content of Conjugated Estrogens, which can be used to support a demonstration of active ingredient sameness. See *Draft Guidance on Conjugated Estrogens* (December 2014), available at: <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>. When final, this guidance will represent FDA’s current thinking on this topic.

³² See 21 CFR 300.50.

Contains Nonbinding Recommendations

Draft — Not for Implementation

174 components, the applicant generally should propose ranges for each molecule in common based
175 on the comparative testing, and provide a justification and/or rationale for acceptability of any
176 component differences between the test product and the reference product (i.e., the presence or
177 absence of any component in the test product compared to the reference product).
178

C. Characterization of the Active Ingredient in the Drug Product

180
181 Typically, the chemical form of the active ingredient in the RLD is the same as the chemical
182 form introduced at the start of drug product manufacture. However, in certain circumstances, the
183 active ingredient may undergo a change in chemical form during drug product manufacture such
184 that the active ingredient is converted to a different chemical form through an intentional or
185 obvious change such that the converted chemical form is present as the active ingredient in the
186 RLD drug product. In such cases, it is the converted chemical form of the active ingredient, as
187 present in the finished dosage form of the RLD, that generally should be used for comparison
188 when demonstrating active ingredient sameness.³³
189

190 When developing a generic drug product, a prospective ANDA applicant generally should look
191 to the approved RLD labeling (e.g., the DOSAGE FORMS AND STRENGTHS,
192 DESCRIPTION, CLINICAL PHARMACOLOGY, and HOW SUPPLIED sections of the
193 labeling) to gain an understanding of the chemical form of the active ingredient in the approved
194 drug product. However, FDA is aware of certain cases in which there may be ambiguity as to
195 the chemical form of an RLD's active ingredient compared to what is described in that RLD's
196 labeling,³⁴ which may, as a scientific matter, result in additional investigations by and
197 information from the prospective ANDA applicant (e.g., comparative testing and scientific
198 rationale) to determine the chemical form of the active ingredient.
199

200 The following is a non-exhaustive list of examples of active ingredient characterization for
201 certain drug products. These examples, and our recommendations, assume there is no ambiguity
202 in the RLD labeling as to the chemical form of the active ingredient, as described above.
203

204 Examples:
205

³³ If the chemical form (or forms) of the active ingredient do not appear in the drug product formulation in a consistent or known manner, then the demonstration of active ingredient sameness may not be assisted by the general recommendations provided in this guidance, and a prospective ANDA applicant may contact the Office of Generic Drugs during drug product development. See section III.D.

³⁴ See, e.g., Letter from J. Woodcock to R.A. Dormer, RE: Vascepa (icosapent ethyl) Capsules (NDA 202057) Exclusivity Determination (May 31, 2016), at 2 (noting that Lovaza's labeling lists "omega-3-acid ethyl esters" as the active ingredient, "which could suggest that Lovaza's active ingredient is its omega-3-acid ethyl ester component" but "FDA defined the drug's active ingredient as the entire [fish oil] mixture at the time of approval," which included ethyl esters of eicosapentaenoic acid and docosahexaenoic acid, among several other minor compounds) (letter is part of the administrative and correspondence document record found at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202057Orig1s000AdminCorresedt3.pdf); see also Letter from Patrizia Cavazzoni to Areta Kupchyk, Docket No. FDA-2016-P-1163 (May 26, 2021) (concluding that the active ingredient in Velphoro is ferric oxyhydroxide, not sucroferric oxyhydroxide, as indicated on the approved drug product labeling) (https://downloads.regulations.gov/FDA-2016-P-1163-0097/attachment_1.pdf).

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 206
- 207
- 208
- 209
- 210
- 211
- 212
- 213
- 214
- 215
- 216
- 217
- 218
- 219
- 220
- 221
- 222
- 223
- 224
- 225
- 226
- 227
- 228
- 229
- 230
- 231
- 232
- 233
- 234
- 235
- 236
- 237
- 238
- 239
- 240
- The portions of a molecule that cause a drug to be an ester or salt are considered to be part of the active ingredient.³⁵ Therefore, the salt or ester form of the active ingredient in the proposed generic drug product must be the same as that in the RLD it references.³⁶ If the RLD labeling states that there are two or more salt or ester forms in the drug product that are known to be present in consistent and reproducible proportions, then the ANDA generally should contain the same salt or ester forms in the same proportions as described in the RLD labeling.³⁷
 - In general, a complex, clathrate, or chelate will be considered part of the active ingredient only if the complex, clathrate, or chelate is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease associated with the approved use of the drug product.³⁸
 - In general, the active ingredient for solid oral dosage forms (e.g., orally disintegrating tablets) will not be considered to include a complex-forming excipient so long as that excipient is not intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease associated with the approved use of the drug product. For example, a weak complex formed with the active ingredient solely to reduce or slow contact of the active ingredient with the tongue by a few seconds to mask an unpleasant taste (taste-masking) would generally not be considered part of the active ingredient. This includes ionic polymers (e.g., polystyrene sulfonate) that form a complex with the active ingredient. Often these polymers are employed for the purpose of taste-masking, such as in risperidone orally disintegrating tablets, or to modulate oral drug release. These polymers may bind to the active ingredient via an ionic interaction which is poorly defined (e.g., non-stoichiometric) and thus do not constitute a new active ingredient salt form. As such, these ionic polymers would generally not be considered part of the active ingredient.
 - In general, carbohydrates (e.g., starch) used to form complexes with the active ingredient in order to stabilize the active ingredient and facilitate bulk processing of the active ingredient and enable the manufacture of the drug product, would not be considered part of the active ingredient. In some cases,

³⁵ See, e.g., § 314.3 (defining *pharmaceutical equivalents* as “drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety . . .”).

³⁶ See section 505(j)(2)(A)(ii) of the FD&C Act.

³⁷ See generally *id.*

³⁸ A prospective applicant seeking assistance in developing a product that may include a complex, clathrate, or chelate is encouraged to contact the Agency during product development via the methods described in section III.D. of this guidance.

Contains Nonbinding Recommendations

Draft — Not for Implementation

241 carbohydrate complexes are formed such that the entire complex is necessary
242 to function in the intended therapeutic manner (e.g., ferumoxytol). In these
243 instances, the complexed carbohydrate would be considered to be part of the
244 active ingredient.

245
246 ○ In general, clathrate forms do not constitute new chemical forms that are
247 considered in determining active ingredient sameness because they are not
248 intended to furnish pharmacological activity or other direct effect in the
249 diagnosis, cure, mitigation, treatment, or prevention of disease associated with
250 the approved use of the drug product.³⁹ For example, although ethinyl
251 estradiol (in drospirenone/ethinyl estradiol tablets) is stabilized by the β -
252 cyclodextrin as a clathrate, this is not considered a different active ingredient
253 from its non-clathrate form that appears in oral dosage forms.

254
255 ○ In general, the active ingredient in gadolinium products is considered to be the
256 entire complexed molecule of gadolinium. Gadolinium products used in
257 medical imaging require that the intact gadolinium complex does not
258 dissociate to liberate free gadolinium ion, which is extremely toxic, and are
259 designed to be tenacious complexes with minute liberation of free gadolinium
260 ion. In addition, the entire complex impacts tissue distribution and thereby
261 impacts its ability to furnish its direct effect as an imaging agent for diagnostic
262 purposes.

D. Additional Recommendations

263
264
265
266 Prospective ANDA applicants are encouraged to review product-specific guidances for generic
267 drug development, which may include recommendations on how to demonstrate active
268 ingredient sameness.⁴⁰ In those guidances, FDA may recommend specific testing for an
269 applicant to demonstrate active ingredient sameness. For example, FDA has recommended
270 pharmacodynamic data to support a demonstration of active ingredient sameness, and also may,
271 in certain situations, recommend pharmacokinetic studies to adequately characterize an active
272 ingredient.
273

³⁹ For example, in a formulation of cetirizine hydrochloride chewable tablets, the active ingredient was formulated as a cyclodextrin clathrate to mask the bitter taste of the cetirizine hydrochloride. See Walsh, J. et al, "Playing hide and seek with poorly tasting paediatric medicines: Do not forget the excipients," *Advanced Drug Delivery Reviews*, Vol. 73, June 30, 2014, pp. 14–33, available at: <https://www.sciencedirect.com/science/article/pii/S0169409X14000349>. For this product, cetirizine hydrochloride was regarded as the chemical form of the active ingredient with β -cyclodextrin (Betadex) constituting an inactive ingredient in the formulation. See FDA Clinical Pharmacology Biopharmaceutics Review(s) and Printed Draft Labeling for Zyrtec Chewable Tablets (NDA 021621), dated March 16, 2004, available at: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>.

⁴⁰ See, for example, the draft product-specific guidance for industry on enoxaparin sodium injection (October 2011), which includes equivalence of in vivo pharmacodynamic profile as one of the five recommended criteria for demonstrating active ingredient sameness of the test and reference products. When final, this guidance will represent FDA's current thinking on this topic. Product-specific guidances are available at: <https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

274 As scientific understanding and technology evolve, FDA will continue to assist in and support
275 the adequate characterization of an active ingredient so that prospective ANDA applicants may
276 adequately demonstrate sameness. In addition, prospective ANDA applicants may submit
277 controlled correspondence⁴¹ to or request a pre-ANDA meeting⁴² with the Office of Generic
278 Drugs to discuss their proposed methods for demonstrating sameness.

⁴¹ Controlled correspondence is appropriate if an applicant has a specific and targeted inquiry about the generic drug development process. See the guidance for industry *Controlled Correspondence Related to Generic Drug Development* (December 2020) for information on the types of inquiries accepted as controlled correspondence and on how to submit controlled correspondence to the Office of Generic Drugs.

⁴² A pre-ANDA meeting is appropriate for a prospective applicant seeking a dialogue with the Agency on a particular matter that would fall outside the scope of controlled correspondence. See the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022) for information on the enhanced pathway for discussions between FDA and a prospective applicant preparing to submit an ANDA for a complex product as defined in the guidance.