
Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn Guidance for Industry

DRAFT GUIDANCE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)**

**July 2016
Generics**

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**U.S. Department of Health and Human Services
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1 **Updating ANDA Labeling After the Marketing Application for the**
2 **Reference Listed Drug Has Been Withdrawn**
3 **Guidance for Industry¹**
4

5
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
8 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
9 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
10 for this guidance as listed on the title page.
11

12
13
14
15 **I. INTRODUCTION**
16

17 This guidance describes a process for updating labeling for abbreviated new drug applications
18 (ANDAs) in cases where FDA has withdrawn approval of the new drug application (NDA)² for
19 the ANDA's reference listed drug (RLD)³ for reasons other than safety or effectiveness. Where
20 approval of the NDA for the RLD has been withdrawn by FDA under these circumstances
21 (referred to in this guidance as a "withdrawn RLD"), and ANDAs are pending or generic drugs
22 continue to be marketed under one or more ANDAs that rely on the withdrawn RLD, the
23 labeling of those pending or marketed ANDA products may need to be updated to reflect
24 changes that would have been necessary had the NDA for the RLD not been withdrawn.
25

26 This guidance sets forth ways in which FDA may seek to facilitate the revision of labeling to
27 reflect updated information for ANDAs that rely on withdrawn RLDs. This guidance will be of
28 interest to the holders of pending or approved ANDAs that rely upon a withdrawn RLD, as well
29 as to applicants seeking to submit ANDAs relying on withdrawn RLDs. We anticipate that this
30 guidance will help facilitate labeling updates for approved ANDAs as well as the approval of
31 certain pending ANDAs where the NDA for the RLD has been withdrawn.
32

33 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
34 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
35 as recommendations, unless specific regulatory or statutory requirements are cited. The use of

¹ This guidance has been prepared by the Office of Regulatory Policy, the Office of Generic Drugs, the Office of New Drugs, and the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research at the Food and Drug Administration.

² For purposes of this guidance, we use the phrase "new drug application" or "NDA" to refer to an application approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(c)), including applications based on a finding of effectiveness under the Drug Efficacy Study Implementation (DESI) review process.

³ See 21 CFR 314.3 (defining reference listed drug and listed drug); see also "Abbreviated New Drug Applications and 505(b)(2) Applications" (Proposed Rule), 80 FR 6802 at 6814 (February 6, 2015).

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36 the word *should* in Agency guidances means that something is suggested or recommended, but
37 not required.

38
39

40 **II. BACKGROUND**

41
42 A generic drug is required to have the same labeling as the RLD at the time of approval, except
43 for changes required because of differences approved under a suitability petition (see section
44 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93) or because the generic drug and the RLD are
45 “produced or distributed by different manufacturers” (see section 505(j)(2)(A)(v) of the FD&C
46 Act). FDA regulations provide examples of permissible differences in labeling that may result
47 where a proposed generic drug and the RLD are “produced or distributed by different
48 manufacturers,” including the omission of an indication or other aspect of labeling protected by
49 patent or exclusivity and “labeling revisions made to comply with current FDA labeling
50 guidelines or other guidance.” 21 CFR 314.94(a)(8)(iv).

51
52 As a general matter, all holders of marketing applications for drug products (both NDAs and
53 ANDAs) have an ongoing obligation to ensure their product labeling is accurate, and not false or
54 misleading. When new information becomes available that causes the labeling to become
55 inaccurate, false or misleading, the application holder must take steps to update its labeling (see,
56 e.g., 21 CFR 201.56(a)(2)). Any drug is misbranded if its labeling is false or misleading, or does
57 not provide adequate directions for use and adequate warnings (sections 301(a) and (b), and
58 502(a), (f), and (j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 331(a)
59 and (b), and 352(a), (f), and (j))).

60
61 Where the NDA for the RLD has not been withdrawn, RLD holders often propose changes to the
62 labeling by submitting them to the NDA. ANDA holders are expected to update their labeling
63 after FDA has approved relevant changes to the labeling for the corresponding NDA RLD. FDA
64 may withdraw approval of an ANDA if it finds that the labeling for the drug product that is the
65 subject of the ANDA is no longer consistent with that for the RLD (section 505(e) of the FD&C
66 Act and 21 CFR 314.150(b)(10)).

67
68 FDA believes ANDA applicants are familiar with the mechanisms for updating labeling for
69 pending and marketed ANDAs where the NDAs for the RLDs have not been withdrawn.
70 However, there has been confusion regarding the process for updating labeling for ANDAs
71 referencing RLDs where the NDAs have been withdrawn.

72
73 NDAs for RLDs may be withdrawn voluntarily, at the NDA holder’s request, for reasons other
74 than safety and effectiveness. Specifically, FDA will withdraw approval of an NDA at the
75 applicant’s request where the drug that is the subject of the application is no longer being
76 marketed, and if certain other conditions are satisfied, including the absence of any FDA finding
77 that the drug is unsafe or ineffective for its approved conditions of use (see, e.g., § 314.150(c)

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78 (21 CFR 314.150(c)).⁴ As noted above, withdrawal of an NDA RLD under these circumstances
79 is referred to in this guidance as a “withdrawn RLD.”⁵

80
81 Where an RLD has been withdrawn, ANDA products that were approved in reliance on the
82 withdrawn RLD may continue to be marketed, and new ANDAs must refer to the withdrawn
83 RLD as the basis for ANDA submission (provided that there has been a determination that the
84 NDA RLD was not withdrawn for reasons of safety or effectiveness) (see § 314.122(c) (21 CFR
85 314.122(c))).

86
87 Under these circumstances, where approval of the NDA for an RLD has been withdrawn, the
88 NDA holder can no longer update labeling for the withdrawn RLD.⁶ Yet as a drug is used over
89 time, the scientific community’s understanding of the drug may evolve based on data from
90 various sources, including published literature and postmarketing data. Therefore, the labeling
91 of ANDAs that rely on the withdrawn RLD might eventually become inaccurate and outdated,
92 resulting in labeling that is false and/or misleading, for example. Likewise, new original
93 ANDAs that rely on the withdrawn RLD might include proposed labeling based on the last
94 approved RLD labeling that includes outdated information that is false and/or misleading.

95
96 If an NDA for a certain drug has been withdrawn, there may be other drugs that contain the same
97 active ingredient (or an active ingredient in the same pharmacologic or therapeutic class) for
98 which approval of the NDA has not been withdrawn. The labeling of those other drugs, as well
99 as the labeling of any corresponding ANDAs, may have been updated to reflect any new
100 scientific information that is needed for the safe and effective use of the drug. This creates a
101 situation in which certain NDAs and ANDAs for a given active ingredient have up-to-date
102 labeling, while other ANDAs do not, simply because those other ANDAs rely on an RLD for
103 which approval of the NDA has been withdrawn. In such cases the labeling of pending ANDAs
104 or marketed ANDAs products may need to be updated to reflect changes that would have been
105 necessary had the NDA for the RLD not been withdrawn.
106

⁴ If the NDA for the RLD has been withdrawn for reasons other than safety or effectiveness, a therapeutically equivalent drug product approved under an ANDA may be designated as the reference standard for use in conducting an in vivo study to demonstrate bioequivalence.

⁵ Withdrawal of approval of an NDA is considered effective upon the date specified in the notice of withdrawal published in the Federal Register. Until that date, an NDA holder that has submitted a request under 21 CFR 314.150 to withdraw the approval of an NDA will continue to be responsible for ensuring that the labeling of the drug product approved under the NDA remains accurate and up to date.

⁶ In cases where marketing of the RLD product has been discontinued but approval of the NDA has not been withdrawn under § 314.150 or section 505(e) of the FD&C Act (referred to in this guidance as a “discontinued RLD”), the NDA holder must still comply with applicable statutory and regulatory requirements. These requirements include, for example, proposing any necessary revisions to update product labeling for the discontinued RLD (see, e.g., § 201.56(a)(2)). ANDA products approved in reliance on a discontinued RLD may continue to be marketed, and new ANDAs must refer to the discontinued RLD as the basis for ANDA submission (see § 314.122(c)). The Agency will continue to list discontinued RLD drug products on the “Discontinued Drug Product List” in FDA’s “Approved Drug Products With Therapeutic Equivalence Evaluations” (the “Orange Book”), unless FDA determines that the drug product was withdrawn from sale for reasons of safety or effectiveness, in which case the drug product will be removed from the Orange Book.

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107 In this guidance, FDA clarifies that consistent with the statute, where the RLD is withdrawn,
108 certain labeling changes may continue to be made for pending ANDAs and marketed ANDAs.⁷
109

110

111 III. SCOPE OF GUIDANCE

112

113 This guidance is limited to labeling updates for generic drugs that are the subject of new original,
114 pending ANDAs or approved ANDAs that rely on an RLD for which approval of the NDA has
115 been withdrawn for reasons other than safety or effectiveness.

116

117 Consistent with this guidance, FDA may seek to facilitate certain updates to the labeling for a
118 new original, pending ANDA or an already-approved ANDA that relies on a withdrawn RLD
119 when the previously approved labeling for the withdrawn RLD has become outdated and such
120 changes would have been necessary had the RLD not been withdrawn.

121

122 The process described in this guidance is intended to complement existing Agency authorities
123 and processes, including FDA’s authority under the Food and Drug Administration Amendments
124 Act of 2007 (FDAAA) to require certain safety labeling changes (SLCs) to the labeling of certain
125 prescription drug products. The relationship of this guidance to certain existing FDA authorities
126 and processes is further discussed in section IV.C below.

127

128

129 IV. UPDATING LABELING OF ANDAs THAT RELY ON WITHDRAWN RLDs

130

131 ANDA holders are responsible for reviewing postmarketing data and published literature as
132 appropriate to satisfy applicable reporting requirements (e.g., 21 CFR 314.81, 314.98).
133 However, FDA (as well as ANDA holders and applicants) may be aware of data relevant to
134 labeling updates in a variety of situations. For example, relevant data may already be reflected in
135 the updated labeling of other drugs in the same pharmacologic or therapeutic class (e.g., class
136 labeling); in non-product specific literature; or in postmarketing information. The updates
137 contemplated by this guidance generally would not involve reliance on product-specific,
138 proprietary information about another drug. Any changes proposed under this guidance must be
139 consistent with the requirement that an ANDA include sufficient information to show that the
140 conditions of use have been previously approved for the RLD (section 505(j)(2)(A)(i)).

141

⁷ The approach proposed in this guidance is consistent with FDA statements made in the context of determinations that certain drug products that have been withdrawn from sale were not withdrawn for reasons of safety or effectiveness, including statements to the effect that “[i]f FDA determines that labeling for these drug products should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.” *See, e.g.*, 80 FR 27320 at 27321 (May 13, 2015) (determining that SODIUM SULAMYD (sulfacetamide sodium) Ophthalmic Solution and Ophthalmic Ointment were not withdrawn from sale for reasons of safety or effectiveness).

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A. Examples of Labeling Updates for ANDAs That Rely on Withdrawn RLDs

In general, the labeling changes contemplated under this guidance include changes necessary to ensure that labeling adequately describes information essential for safe and effective use; that labeling is accurate and meets current standards; and that labeling is not false or misleading under section 502 of the FD&C Act. Revisions described by this guidance may include changes based on data that have become available since the RLD was withdrawn, including published literature and other data that emerge after products have entered the market.

More specifically, the labeling changes contemplated under this guidance may be needed:

- To achieve consistency with the labeling of other products that have the same active ingredient or an active ingredient in the same pharmacologic or therapeutic class, or with the labeling of other products approved for the same indication, where appropriate;
- To correct outdated information related to a previously approved indication; and/or
- To achieve consistency with applicable regulations and current FDA labeling guidelines or other guidance (as already contemplated under § 314.94(a)(8)(iv)).

Examples of the updates contemplated by this guidance might include the following (this list is not intended to be exhaustive):⁸

- Updating the indication statement in the INDICATIONS AND USAGE section to reflect current disease terminology (e.g., changing “Juvenile Rheumatoid Arthritis” to “Juvenile Idiopathic Arthritis”) or to modify the description of an outdated restriction on the use of the drug in specific situations.
- For systemic antibacterial drug products, including the required statement about antimicrobial resistance in the INDICATIONS AND USAGE section (see 21 CFR 201.24(b)).
- For parenteral products, including the following required statement or appropriate modification in the DOSAGE AND ADMINISTRATION section: “Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit” (see 21 CFR 201.57(c)(3)(iv)).
- Removing a risk from the CONTRAINDICATIONS section if the benefit outweighs the risk of use in the situation or subpopulation (e.g., the risk is theoretical) (see 21 CFR 201.57(c)(5)).

⁸ FDA intends to use the process outlined in section IV.B to address these types of labeling changes, unless, in particular circumstances, such changes fall within FDA’s authority to require SLCs pursuant to section 505(o)(4) of the FD&C Act. As noted above in section III, the process described in this guidance is intended to complement existing Agency authorities and processes, including FDA’s authority to require SLCs.

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- 181 • Revising the WARNINGS AND PRECAUTIONS section to include current steps to
182 prevent, mitigate, monitor for, or manage a clinically significant adverse reaction or risk.
183
- 184 • Revising the ADVERSE REACTIONS section to include a new adverse reaction based
185 on postmarketing experience.
186
- 187 • Revising the ADVERSE REACTIONS section to include the following recommended
188 statement or appropriate modification before the presentation of adverse reactions from
189 spontaneous reports:
190

191 *The following adverse reactions have been identified during postapproval*
192 *use of drug X. Because these reactions are reported voluntarily from a*
193 *population of uncertain size, it is not always possible to reliably estimate*
194 *their frequency or establish a causal relationship to drug exposure.*
195

196 *See FDA guidance for industry, Adverse Reactions Section of Labeling for Human*
197 *Prescription Drug and Biological Products — Content and Format.*⁹
198

- 199 • Adding a new clinically significant drug interaction in the DRUG INTERACTIONS
200 section based on postmarketing data showing that a newly approved product interacts
201 with the active ingredient in the ANDA product or with products in the ANDA product's
202 class.
203
- 204 • Revising the OVERDOSAGE section to include overdose management strategies that are
205 consistent with current Poison Control recommendations.
206
- 207 • For systemic antibacterial drug products, updating susceptibility test interpretive criteria,
208 susceptibility test methods, and quality control parameters in the *Microbiology* subsection
209 of the CLINICAL PHARMACOLOGY section. *See FDA guidance for industry,*
210 *Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug*
211 *Products and Antimicrobial Susceptibility Testing Devices;*¹⁰ see also section 1111 of
212 FDAAA.
213
- 214 • Making changes to keep up to date with class Medication Guides (e.g., if there is a class
215 Medication Guide for nonsteroidal anti-inflammatory drugs (NSAIDs), all ANDA
216 NSAID products -- including those with withdrawn NDA RLDs -- should have the
217 current version of the class NSAID Medication Guide).
218
- 219 • Making changes requested by FDA prior to withdrawal of an NDA RLD that are
220 determined to be necessary for safe and effective use.

⁹ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

¹⁰ Available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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- 221
222 • Making changes or updates described in Agency regulations, guidance, or Federal
223 Register notices even if they do not specifically address the labeling of ANDAs where the
224 NDA RLD is withdrawn.
225

B. Process for Labeling Updates

226
227
228 ANDA holders have the ability to submit any of the labeling updates contemplated by this
229 guidance, i.e. those changes needed to ensure that labeling is accurate and meets current
230 standards for an ANDA whose RLD is withdrawn, through the submission of a prior approval
231 supplement (PAS). If FDA determines that a change proposed in this manner is appropriate and
232 approves the supplement, the Agency may request that other ANDA holders and any ANDA
233 applicants relying on the same withdrawn RLD make the same updates, where appropriate. This
234 latter step is intended to ensure that labeling remains uniform across generic drugs that rely on
235 the same RLD.
236

237 FDA may also request a changes being effected (CBE-0) supplement from ANDA holders (see
238 21 CFR 314.70(c)(6)(iii)(E)) if FDA becomes aware of labeling updates that are needed to
239 ensure that labeling is accurate and meets current standards for an ANDA or ANDAs whose
240 RLD is withdrawn.¹¹ Under these circumstances, the Agency would also solicit an amendment
241 reflecting the needed updates from any ANDA applicants seeking initial approval that rely on the
242 same RLD. Such an amendment would be necessary prior to ANDA approval.
243

C. Relationship of This Guidance to Existing Authorities and Processes

244
245
246 The process described in this guidance is intended to complement existing Agency authorities
247 and processes. Two of these are described below.
248

1. Safety Labeling Changes Under Section 505(o)(4) of the FD&C Act

249
250
251 The Food and Drug Administration Amendments Act of 2007 (FDAAA) gave FDA explicit
252 authority to require certain safety labeling changes (SLCs) to the labeling of prescription drug
253 products marketed under NDAs and under ANDAs whose RLD is not currently marketed (i.e.,
254 ANDAs with a “withdrawn RLD” or “discontinued RLD” as described in the Background
255 section of this guidance). If FDA becomes aware of “new safety information”¹² that it believes

¹¹ FDA has issued a proposed rule that would allow ANDA holders to independently submit CBE-0 supplements making certain safety-related updates to their labeling, based on newly acquired information. *See* 78 FR 67985 (November 13, 2013). That proposed rule, along with comments received, remains under review. If the proposed rule is finalized, the final rule will govern the process for carrying out labeling updates that are within the scope of the rule. The process described in this guidance would not alter ANDA holders’ obligation to maintain up-to-date labeling, whether under the current regulatory framework or a future scenario at such time as the proposed rule is finalized.

¹² *See* 21 U.S.C. 355-1(b)(3). The term “new safety information” includes certain information about a serious risk or an unexpected serious risk associated with the use of a drug that FDA has become aware of since the drug was approved, since a risk evaluation and mitigation strategy (REMS) was required, or since the last assessment of the approved REMS for the drug.

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256 should be included in labeling, FDA issues a safety labeling change notification letter, which
257 may include proposed labeling changes, to the affected application holder(s) (see section
258 505(o)(4) of the FD&C Act). Application holders must then submit either a supplement with the
259 proposed labeling changes, or a rebuttal statement explaining why the proposed changes are not
260 warranted, within 30 days. FDA reviews and acts on these supplements and rebuttal statement
261 within defined time frames (see FDA guidance for industry, *Safety Labeling Changes –*
262 *Implementation of Section 505(o)(4) of the FD&C Act.*¹³

263 The FDAAA SLC process is separate and distinct from the process described in this guidance.
264 FDA will continue to use its FDAAA SLC authorities where appropriate in situations where
265 FDA becomes aware of “new safety information” about a serious risk or an unexpected serious
266 risk that the Agency believes should be included in product labeling.

267 This guidance addresses certain situations in which needed updates to the labeling of ANDAs
268 that rely on withdrawn RLDs may not be captured by the FDAAA SLC process. For example:

- 269 • The FDAAA SLC authorities apply only to approved NDAs and ANDAs. When new
270 original ANDAs are submitted that rely on a withdrawn RLD, the FDAAA SLC
271 authorities do not extend to the draft labeling submitted as part of those pending
272 applications. Under this guidance, FDA will consider the FDAAA SLC notification that
273 is sent to the holders of approved applications to be “FDA labeling guidelines or other
274 guidance” within the meaning of § 314.94(a)(8)(iv). Applicants with pending ANDAs
275 will be able to submit amendments to their applications with labeling that reflects the
276 safety labeling change made by the holders of approved ANDAs relying on the same
277 RLD, and this will be considered a change made to comply with “current FDA labeling
278 guidelines or other guidance” within the meaning of the regulation.
279
- 280 • Before FDAAA came into effect on March 25, 2008, certain labeling updates had been
281 accomplished through other regulatory procedures, including class labeling changes.
282 Those updates were typically carried out in the first instance by updates to NDA RLD
283 labeling that would then have been reflected in the labeling of ANDAs relying on that
284 RLD. Where an RLD affected by the update was withdrawn, however, the corresponding
285 ANDAs may have never adopted these updates. Where appropriate under the process
286 described in this guidance (for example where labeling changes are not implemented
287 through the FDAAA SLC process), FDA will ask ANDA holders that rely on withdrawn
288 RLDs to make these updates to their labeling consistent with this guidance.
289

290 2. *Section 409I of the Public Health Service Act*

291
292 Under section 409I of the Public Health Service Act (42 U.S.C. § 284m), the National Institutes
293 of Health (NIH) and FDA implement a program for pediatric studies of drugs. NIH may under
294 certain circumstances award funds to an entity with appropriate expertise for the conduct of
295 studies needed to provide safety and efficacy information for pediatric labeling. Upon

¹³ Available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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296 completion of these pediatric studies, a study report that includes all data generated in connection
297 with the studies is placed in a public docket assigned by FDA. FDA will review the data
298 generated, and if labeling changes are determined to be appropriate, FDA may request CBE-0
299 supplements from the affected application holders to reflect those changes. Affected application
300 holders may include holders of ANDAs that rely on withdrawn RLDs.

301
302 The section 409I process will not be affected by this guidance.

303
304