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# Guidance for Industry

## Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications

### *DRAFT GUIDANCE*

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For questions on the content of the draft document contact Cecelia M. Parise, 301-827-5845.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
October 2000  
OGD

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*Additional copies of this Draft Guidance are available from:*

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
October 2000  
OGD**

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*Draft – Not for Implementation*

**GUIDANCE FOR INDUSTRY<sup>1</sup>**

**Referencing Discontinued Labeling  
for Listed Drugs in Abbreviated  
New Drug Applications**

This draft guidance, when finalized, will represent the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

*If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:*

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed changes.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

**I. INTRODUCTION**

This document is intended to provide guidance to applicants on referencing discontinued labeling for listed drugs in abbreviated new drug applications (ANDAs) submitted for approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act). This issue is not addressed directly in the regulations governing the approvals of ANDAs at 21 CFR 314 subpart C. The Office of Generic Drugs (OGD) is proposing the most appropriate response to this regulatory question, and is making its current thinking on the matter available to the public through this guidance.

**II. BACKGROUND**

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman amendments) established the generic drug approval program used today to ensure that lower price generic drugs are made available to the public promptly upon the expiration of patent and exclusivity protections covering the innovator products. The generic drug approval process generally depends on the ANDA applicant establishing that the generic drug is the same as an approved innovator product (the listed drug) with respect to active ingredient, dosage form, strength, route of administration, conditions of use, and labeling.

<sup>1</sup> This draft guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER).

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42  
43 During the period when an innovator drug is being marketed, it may undergo a number of  
44 changes that are approved through new drug application (NDA) supplements. Such  
45 changes can include the addition of new indications, changes to the product formulation,  
46 and labeling changes. In the past, when ANDAs have been submitted, they have  
47 referenced only the innovator drug product labeling as it appears at the time of ANDA  
48 submission. However, recently a question has been raised as to whether, in certain  
49 circumstances, an ANDA can refer to discontinued labeling for the listed drug.

50  
51 The issue of referencing discontinued labeling for the listed drug arises when the sponsor  
52 of the innovator drug product has obtained exclusivity or patent protection for a new  
53 aspect of product labeling and has removed the previous unprotected labeling for reasons  
54 other than safety or effectiveness. When the holder of the innovator drug obtains  
55 approval and market protection for a change to the drug and removes the corresponding  
56 unprotected information from the current labeling, there is no current complete labeling  
57 for the ANDA applicant to reference.<sup>2</sup> For example, the NDA holder may obtain  
58 approval and market protection for a new dosing regimen and remove the previous  
59 dosing regimen(s) from the labeling. In this situation, the ANDA applicant, which must  
60 include information regarding dosing regimen in its application, is blocked by the NDA  
61 holder's exclusivity from referencing the new dosing regimen contained in the innovator  
62 drug labeling, and all the previous dosing regimen information has been removed from  
63 the current labeling. This raises the question of whether applicants will be barred from  
64 obtaining approval for any ANDA for that innovator drug until the protection for the new  
65 dosing regimen expires, because relevant labeling is either protected or has been removed  
66 from the currently marketed product.<sup>3</sup>

67  
68 In FDA's view, the appropriate approach to the situation depends on whether the previous  
69 labeling was withdrawn from the drug product for reasons of safety or effectiveness, and  
70 whether omission of the protected information will render the drug unsafe. This is the  
71 same approach taken by the Agency when an entire product, rather than just a portion of  
72 the labeling, is withdrawn from the market, and when a portion of the innovator labeling  
73 must be omitted from a generic drug label because of patent or exclusivity protection.

74  
75 FDA's proposed approach creates a process intended to assure that labeling removed  
76 from an innovator drug product for reasons of safety or effectiveness cannot be  
77 referenced in an ANDA. At the same time, this process will permit approval of ANDAs

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<sup>2</sup> Contrast this with the situation in which an innovator has obtained approval for a new indication and patent or exclusivity protection that extends beyond the protection for other indications that remain on the labeling. The ANDA applicant may cite the innovator labeling that includes all of the approved indications, and only the protected indication will be omitted from the ANDA labeling when it is approved. *See Bristol-Myers Squibb v. Shalala*, 91 F.3d 1493 (D.C.Cir. 1996).

<sup>3</sup> In theory, the innovator could delay generic competition indefinitely by continuing to make minor — but protectable — changes to the drug, and removing unprotected labeling. If this approach were effective, the Agency also could expect to review many more labeling supplements, possibly for changes that, although sufficiently innovative to warrant patent or exclusivity protection, do not necessarily represent significant improvements in the currently marketed drug.

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78 that reference labeling that, although removed from the currently marketed innovator  
79 product, nonetheless describes the safe and effective use of the drug. This approach will  
80 make safe and effective generic drug products available to the public as promptly as  
81 possible when relevant market protections have expired.

### 82 83 **III. PROPOSED APPROACH**

84  
85 The Agency has determined that in certain circumstances an ANDA should be permitted  
86 to reference discontinued labeling for a listed drug. This generally should occur when:

- 87  
88 1. The holder of the NDA for the innovator drug has obtained approval for a change in  
89 the drug labeling.
- 90  
91 2. That change has received either a patent listed in *Approved Drug Products with*  
92 *Therapeutic Equivalence Evaluations* (the *Orange Book*) or market exclusivity under  
93 the Act.
- 94  
95 3. The NDA sponsor has removed or revised the labeling describing the corresponding  
96 unprotected aspects of the drug.
- 97  
98 4. The change to the drug product is not one for which a suitability petition may be filed  
99 (21 CFR 314.93).
- 100  
101 5. The sponsor wishing to reference the discontinued labeling has submitted a petition  
102 requesting that the Agency determine whether the previous labeling was withdrawn  
103 for reasons of safety or effectiveness, or the Agency has undertaken its own inquiry  
104 regarding the withdrawal of the previous labeling.
- 105  
106 6. The Agency has determined that the previous innovator labeling was not withdrawn  
107 for reasons of safety or effectiveness.
- 108  
109 7. The Agency has determined that omission of the protected information will not render  
110 the drug product less safe or effective than the currently marketed innovator product.

### 111 112 113 **IV. SUBMISSION OF ANDAS**

#### 114 115 **A. Statutory Requirements**

116  
117 The generic drug approval process is based on the ANDA applicant establishing that its  
118 product is the same as a drug previously approved by FDA. Among other things, an  
119 ANDA must provide information to show that the conditions of use, route of  
120 administration, dosage form, and strength of the proposed product have been previously  
121 approved for a listed drug (section 505(j)(2)(A) of the Act). If an ANDA applicant wants  
122 approval of a change to the route of administration, dosage form, strength, or the  
123 substitution of an active ingredient in a combination drug product, it can obtain approval

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124 for this change through a suitability petition (section 505(j)(2)(C)). The ANDA also must  
125 include information to show that the labeling for the proposed drug is the same as the  
126 labeling approved for the listed drug, except for differences approved through a petition,  
127 or because the proposed drug and listed drug are produced by different manufacturers  
128 (section 505(j)(2)(A)(v)).  
129

130 A listed drug is a drug included on a list published by FDA of drugs approved for safety  
131 and effectiveness under section 505(c) (section 505(j)(7)) of the Act. This list is  
132 published in the *Orange Book*. A drug whose approval was withdrawn or suspended  
133 under section 505(e) for reasons of safety or effectiveness, or that has been withdrawn  
134 from sale for reasons of safety or effectiveness, cannot serve as a listed drug for approval  
135 and is removed from the *Orange Book* (section 505(j)(4)(I) and (j)(7)(C)).  
136

### 137 B. Regulatory Requirements 138

139 Identification of a listed drug is a crucial component of the ANDA approval process. An  
140 ANDA must refer to a listed drug (21 CFR 314.94(a)(3)). The characteristics and  
141 labeling of the listed drug generally will be duplicated in the characteristics and labeling  
142 of the product proposed in the ANDA (21 CFR 314.94(a)(3)-(9)). A drug approved in an  
143 ANDA must be the same as the listed drug in terms of active ingredient(s), dosage form,  
144 strength, route of administration, and conditions of use, except for conditions of use for  
145 which approval cannot be granted because of exclusivity or an existing patent (21 CFR  
146 314.92(a)(1)). Certain differences will be permitted for products for which a suitability  
147 petition has been approved, or because the drug proposed in the ANDA and the listed  
148 drug are produced or distributed by different manufacturers. These differences can  
149 include omission of an indication or other aspect of labeling that is protected by patent or  
150 exclusivity (21 CFR 314.94(a)(8)(iv)). Aspects of a listed drug's labeling that are  
151 protected by patent or exclusivity may be omitted from the labeling proposed in an  
152 ANDA if the resulting differences in the labeling do not render the proposed drug product  
153 less safe or effective for all the remaining, unprotected conditions of use (21 CFR  
154 314.127(a)(7)).  
155

156 An ANDA may refer to a listed drug that is an approved product currently being  
157 marketed, or that is an approved product which has been withdrawn from the market by  
158 the sponsor.<sup>4</sup> If an ANDA applicant references a listed drug that the sponsor has ceased  
159 to market, the FDA must determine whether the drug was removed from the market for  
160 reasons of safety or effectiveness before the ANDA can be approved (21 CFR 314.161).  
161 If the Agency has not made such a determination on its own initiative, the ANDA relying

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<sup>4</sup> FDA regulations define *listed drug* at 21 CFR 314.3(b) as "a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of [the Orange Book], or any current supplement thereto." Note: section 505(j)(5) of the Act has been renumbered as 505(j)(6).

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162 on the discontinued drug must be accompanied by a petition requesting FDA to  
163 determine whether the drug was withdrawn from the market for reasons of safety or  
164 effectiveness (21 CFR 314.122).

165

### **C. Past Practice**

166

167  
168 In the past, when an applicant submitted an ANDA, the only labeling available for the  
169 listed drug has been labeling on the currently marketed form of the listed drug. The  
170 regulations require an ANDA to include a copy of the "currently approved labeling for  
171 the listed drug" (21 CFR 314.94(a)(8)). If the generic product will have labeling that is  
172 different from that of the listed drug, the ANDA applicant should state the reason for  
173 such differences and explain why such differences are permitted. As described above,  
174 certain differences from the innovator labeling are permitted.

175

176 The question of whether an ANDA could refer to previously approved but subsequently  
177 altered labeling had not arisen previously. Therefore, until recently, the Agency had not  
178 had a reason to develop a policy on the appropriate response to this situation.<sup>5</sup> Now, with  
179 what could be a growing practice among innovator sponsors of substituting protected  
180 labeling for unprotected labeling, the Agency has determined that in certain situations, it  
181 may approve an ANDA for a drug product with labeling that was previously approved for  
182 the listed drug, but which the listed drug is no longer carrying.

183

184

### **V. REFERENCING DISCONTINUED LABELING FOR A LISTED DRUG IN AN ANDA**

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186

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189

For an ANDA applicant to refer to discontinued labeling for a listed drug, the following conditions should exist.

190

191

#### **A. Existence of Exclusivity or Patent Protection**

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198

An ANDA generally should refer to discontinued labeling for the listed drug only when, at the time the ANDA is submitted (or while it is pending), an essential part of the labeling for the currently marketed innovator drug is protected by exclusivity or a patent, and the corresponding unprotected labeling has been removed. This approach is based on the desire to minimize confusion in the marketplace arising from the availability of drugs that are the same in many respects, but have slightly different labeling.<sup>6</sup>

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<sup>5</sup> In 1998, the Office of Generic Drugs provided an informal opinion to an innovator company that had removed unprotected dosing information from its label stating that the Agency would not approve an ANDA that does not contain the same dosing and administration information as the listed drug. That opinion, however, was given in a case in which the discontinued labeling information was determined by the Agency to have been removed from the innovator drug for reasons of safety or effectiveness. To address any concern that the approach described in this guidance can be considered a change from past interpretation, the guidance is being released in draft for public comment prior to implementation.

<sup>6</sup> There are already situations in which ANDAs will be approved for drug products that are

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### **B. Identifying Appropriate Labeling**

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201  
202 The ANDA applicant should identify the discontinued labeling for the listed drug to  
203 which it will refer. Generally, this will be the labeling as approved in the innovator  
204 application just prior to the addition of the protected part labeling and deletion of the  
205 unprotected part of labeling.

206

### **C. Submission of Petition Requesting Determination of Reasons for Change to Labeling**

207

208  
209  
210 Once the ANDA applicant has identified the discontinued labeling for the listed drug to  
211 which it will refer, the applicant should submit a petition as described in 21 CFR  
212 314.122, seeking a determination by FDA that the discontinued labeling was not  
213 withdrawn from the listed drug for reasons of safety or effectiveness. An ANDA for the  
214 drug may be submitted at the same time the petition is submitted, but the ANDA will not  
215 be approved until the Agency has determined that the discontinued labeling for the listed  
216 drug was not withdrawn for reasons of safety or effectiveness. FDA also may, on its own  
217 initiative, begin the process of determining whether labeling was discontinued for reasons  
218 of safety or effectiveness.

219

### **D. FDA Determination on Safety and Effectiveness**

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221  
222 The Agency will determine whether the labeling was discontinued for reasons of safety  
223 or effectiveness. If the labeling was discontinued for reasons of safety or effectiveness, it  
224 cannot be referred to by the ANDA applicant. Such a determination will be based on the  
225 same factors and information FDA considers when determining whether a product  
226 withdrawn entirely from the market was withdrawn for reasons of safety or effectiveness  
227 (see 54 FR 28872, 28907-08; July 10, 1989). In addition, the Agency will determine  
228 whether omission of protected information from the labeling would render the proposed  
229 drug product less safe or effective for all the remaining, unprotected conditions of use.<sup>7</sup>  
230 The Agency will publish its determination in the *Federal Register*, as described in 21 CR  
231 314.161.

232

### **E. Therapeutic Equivalence Ratings**

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234  
235 Whether a drug approved in an ANDA that refers to discontinued labeling for the listed  
236 drug will be rated therapeutically equivalent to the currently marketed innovator product  
237 will depend upon the differences in the labeling.

238

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different from the marketed innovator drug. For example, an ANDA may be approved for fewer than all of the indications approved for the innovator drug. There can also be differences in labeling related to excipients, handling and administration of the drug related to excipient differences, and differences arising from revisions in labeling guidelines (21 CFR 314.94(a)(8)(iv)).

<sup>7</sup> New labeling will not be protected by exclusivity if it describes new risks or warnings (54 FR 28872, 28899, July 10, 1989; 59 FR 50338, 50356-57, October 3, 1994).

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239 **F. Expiration of Exclusivity or Patent Protection**

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241 Once the exclusivity or patent protecting the current innovator labeling has expired, the  
242 ANDA applicant whose product references the discontinued labeling should file a  
243 supplement to its ANDA to make the labeling conform to the labeling of the marketed  
244 innovator product.