
Guidance

Marketed Unapproved Drugs — Compliance Policy Guide

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For questions regarding this draft document contact Sakineh Walther 301-827-8964, walthers@cderr.fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 2003

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*Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857
(Phone 301-827-4573)*

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Guidance¹

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This Compliance Policy Guide (CPG) describes how we intend to exercise our enforcement discretion with regard to drugs marketed in the United States that do not have required FDA approval for marketing. This CPG supersedes section 440.100, Marketed New Drugs Without Approved NDAs or ANDAs (CPG 7132c.02). It applies to any new drug required to have FDA approval for marketing, including new drugs covered by the Over the Counter (OTC) Review.

II. BACKGROUND

A. Reason for this Guidance

For historical reasons, some drugs are available in the United States that lack required FDA approval for marketing. A brief informal summary description of the various categories of these drugs and their regulatory status is provided in Appendix A as general background for this document. The manufacturers of these drugs have not received FDA approval to legally market their drugs, nor are the drugs being marketed in accordance with the OTC drug review. The new drug approval and OTC monograph processes play an essential role in ensuring that all drugs are both safe and effective. Manufacturers of new drugs that lack required approval, including those that are not marketed in accordance with an OTC monograph, have not provided FDA with evidence demonstrating that their products are safe and effective, and so we have an interest in

¹ This draft guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

44 taking steps to either encourage the manufacturers of these products to obtain the required
45 evidence and comply with the approval provisions of the Federal Food, Drug, and Cosmetic Act
46 (the Act), or remove the products from the market. We need to achieve these goals without
47 adversely affecting public health, imposing undue burdens on consumers, or unnecessarily
48 disrupting the market.

49
50 The goals of this guidance are to (1) clarify for FDA personnel and the regulated industry how
51 we intend to exercise our enforcement discretion regarding unapproved drugs and (2) emphasize
52 that illegally marketed drugs must obtain FDA approval.

53 54 **B. Historical Enforcement Approach**

55
56 FDA estimates that, in the United States today, perhaps as many as several thousand drug
57 products are marketed illegally without required FDA approval.² Because we do not have
58 complete data on illegally marketed products and because the universe of products is constantly
59 changing as products enter and leave the market, we first have to identify illegally marketed
60 products before we can contemplate enforcement action. Once an illegally marketed product is
61 identified, taking enforcement action against the product would typically involve one or more of
62 the following: requesting voluntary compliance; providing notice of action in a *Federal Register*
63 notice; issuing an untitled letter; issuing a Warning Letter; or initiating a seizure, injunction, or
64 other proceeding. Each of these actions is time-consuming and resource intensive. Recognizing
65 that we are unable to take action immediately against all of these illegally marketed products and
66 that we need to make the best use of scarce Agency resources, we have had to prioritize our
67 enforcement efforts and exercise enforcement discretion with regard to products that remain on
68 the market.

69
70 In general, in recent years, FDA has employed a risk-based enforcement approach with respect to
71 marketed unapproved drugs that includes efforts to identify illegally marketed drugs,
72 prioritization of those drugs according to potential public health concerns or other impacts on the
73 public health, and subsequent regulatory follow-up. Some of the specific actions the Agency has
74 taken have been precipitated by evidence of safety or effectiveness problems that has either come
75 to our attention during inspections or was brought to our attention by outside sources.

76 77 78 **III. FDA'S ENFORCEMENT POLICY**

79
80 In the discussion that follows, we intend to clarify our approach to prioritizing our enforcement
81 actions and exercising our enforcement discretion with regard to the universe of unapproved,
82 illegally marketed drug products in all categories.

² This rough estimate is made up of several hundred drugs in various strengths, combinations, and dosage forms from multiple distributors and repackagers. For example, the FDA recently took action against single-ingredient, extended-release guaifenesin drug products. For this one drug, there were approximately 20 manufacturers and approximately 50 repackagers and private label distributors, many of whom sold multiple single-ingredient, extended-release guaifenesin products.

83
84 **A. Enforcement Priorities**
85

86 Consistent with our risk-based approach to the regulation of pharmaceuticals, FDA intends to
87 continue its current policy of giving higher priority to enforcement actions involving unapproved
88 drug products in the following categories:
89

90 **Drugs with potential safety risks.** Removing potentially unsafe drugs protects the
91 public from direct and indirect health threats.
92

93 **Drugs that lack evidence of effectiveness.** Removing ineffective drugs protects the
94 public from using these products in lieu of effective treatments. Depending on the
95 indication, some ineffective products would, of course, pose safety risks as well.
96

97 **Health fraud drugs.** FDA defines health fraud as "[t]he deceptive promotion,
98 advertisement, distribution or sale of articles . . . that are represented as being effective to
99 diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a
100 beneficial effect on health, but which have not been scientifically proven safe and
101 effective for such purposes. Such practices may be deliberate, or done without adequate
102 knowledge or understanding of the article" (CPG Sec. 120.500). Of highest priority in
103 this area are drugs that present a direct risk to health. Indirect health hazards exist,
104 however, if, as a result of reliance on the product, the consumer is likely to delay or
105 discontinue appropriate medical treatment. FDA's health fraud CPG outlines priorities
106 for evaluating regulatory actions against indirect health hazard products, such as whether
107 the therapeutic claims are significant, whether there are any scientific data to support the
108 safety and effectiveness of the product, and the degree of vulnerability of the prospective
109 user group (CPG Sec. 120.500).
110

111 Drugs that present a challenge to the drug approval or OTC monograph system, directly or
112 indirectly, fall into one or more of the above categories because these systems are designed to
113 avoid the risks associated with potentially unsafe, ineffective, and fraudulent drugs. Targeting
114 drugs that challenge the drug approval or OTC monograph system buttresses the integrity of
115 these systems and makes it more likely that firms will comply with the new drug approval and
116 monograph requirements, which benefits the public health.
117

118 Drugs that present challenges to these systems include drugs that directly compete with an
119 approved drug, such as when a company obtains approval of an NDA for a product that other
120 companies are marketing without approval (see section III.C., Special Circumstances – Newly
121 Approved Product). Also included are drugs marketed in violation of a final OTC monograph
122 that is in effect.
123

124 **B. Notice of Enforcement Action and Continued Marketing of Unapproved**
125 **Drugs**
126

127 **The FDA is not required to, and generally does not intend to, give special notice that a drug**
128 **product may be subject to enforcement action unless FDA determines that such notice is**

129 **necessary or appropriate to protect the public health.**³ **The issuance of this guidance is**
130 **intended to provide notice that any product that is being marketed illegally is subject to**
131 **FDA enforcement action at any time.**⁴ The only exception to this policy is, as set forth
132 elsewhere, that generally products subject to an ongoing DESI⁵ proceeding or ongoing OTC
133 monograph proceeding (i.e., an OTC product that is part of the OTC review for which an
134 effective final monograph is not yet in place) may remain on the market during the pendency of
135 that proceeding⁶ and any period of enforcement discretion (*grace period*) specifically provided in
136 the proceeding (such as a delay in the effective date of a final OTC monograph).⁷ However,
137 once the relevant DESI or OTC monograph proceeding is completed and any specific grace
138 period provided in the proceeding has expired, all products that are not in compliance with the
139 conditions for marketing determined in that proceeding may be subject to enforcement action at
140 any time without further notice (see, e.g., 21 CFR 310.6).

141
142 **FDA intends to evaluate on a case-by-case basis whether justification exists to exercise**
143 **enforcement discretion to allow continued marketing for some period of time after FDA**
144 **determines that a product is being marketed illegally.** In deciding whether to allow such a
145 grace period, we intend to consider the following factors: (1) the effects on the public health of
146 proceeding immediately to remove the illegal products from the market (including whether the
147 product is medically necessary and, if so, the ability of legally marketed products to meet the
148 needs of patients taking the drug); (2) the difficulty associated with conducting any required
149 studies, preparing and submitting applications, and obtaining approval of an application; (3) the
150 burden on affected parties of immediately removing the products from the market; (4) the
151 Agency's available enforcement resources; and (5) any special circumstances relevant to the
152 particular case under consideration.

153 154 **C. Special Circumstances — Newly Approved Product**

155
156 Sometimes, a company may obtain approval of an NDA for a product that other companies are

³ For example, in 1997, FDA issued a *Federal Register* notice declaring all orally administered levothyroxine sodium products to be new drugs and required manufacturers to obtain approved new drug applications (62 FR 43535, August 14, 1997). Nevertheless, FDA gave manufacturers 3 years (later extended to 4 (65 FR 24489, April 26, 2000)) to obtain approved applications and allowed continued marketing without approved new drug applications because FDA found that levothyroxine sodium products were medically necessary to treat hypothyroidism and no alternative drug provided an adequate substitute.

⁴ For example, FDA may take action at any time against a product that was originally marketed before 1938, but that has been changed since 1938 in such a way as to lose its grandfather status.

⁵ The Drug Efficacy Study Implementation (DESI) was the process used by FDA to evaluate for effectiveness for their labeled indications over 3,400 products that were approved only for safety between 1938 and 1962. DESI is explained more fully in the appendix to this document.

⁶ OTC drugs covered by ongoing OTC monograph proceedings may remain on the market as provided in current enforcement policies. See, e.g., CPG section 450.200, 450.300, 21 CFR part 330. This document does not affect the current enforcement policies for such drugs.

⁷ Sometimes, a final OTC monograph may have a delayed effective date or provide for a specific period of time for marketed drugs to come into compliance with the monograph. At the end of that period, drugs that are not marketed in accordance with the monograph will be subject to enforcement action and the exercise of enforcement discretion in the same way as any other drug discussed in this CPG.

157 marketing without approval.⁸ We want to encourage this type of voluntary compliance with the
158 new drug requirements because it benefits the public health by increasing the assurance that
159 marketed drug products are safe and effective — it also reduces the resources FDA must expend
160 on enforcement. Thus, because they present a direct challenge to the drug approval system, FDA
161 is more likely to take enforcement action against remaining unapproved drugs in this kind of
162 situation. However, we will take into account the circumstances once the product is approved in
163 determining how to exercise our enforcement discretion with regard to the unapproved products.
164 In exercising enforcement discretion, we intend to balance the need to provide incentives for
165 voluntary compliance against the implications of enforcement actions on the marketplace and on
166 consumers who are accustomed to using the marketed products.

167
168 When a company obtains approval to market a product that other companies are marketing
169 without approval, FDA normally intends to allow a grace period of roughly 1 year from the date
170 of approval of the product before it will initiate enforcement action (e.g., seizure or injunction)
171 against marketed unapproved products of the same type. However, the grace period provided is
172 expected to vary from this baseline based upon the following factors: (1) the effects on the public
173 health of proceeding immediately to remove the illegal products from the market (including
174 whether the product is medically necessary and, if so, the ability of the holder of the approved
175 application to meet the needs of patients taking the drug); (2) whether the effort to obtain
176 approval was publicly disclosed; (3) the difficulty associated with conducting any required
177 studies, preparing and submitting applications, and obtaining approval of an application; (4) the
178 burden on affected parties of removing the products from the market; (5) the Agency's available
179 enforcement resources; and (6) any other special circumstances relevant to the particular case
180 under consideration.

181
182 The length of any grace period and the nature of any enforcement action taken by the FDA will
183 be decided on a case-by-case basis. Companies should be aware that a Warning Letter may not
184 be sent before initiation of enforcement action and should not expect any grace period that is
185 granted to protect them from the need to leave the market for some period of time while
186 obtaining approval. Companies marketing unapproved new drugs should also recognize that,
187 while FDA normally intends to allow a grace period of roughly 1 year from the date of approval
188 of an unapproved product before it will initiate enforcement action (e.g., seizure or injunction)
189 against others who are marketing that unapproved product, it is possible that a substantially
190 shorter grace period would be provided, depending on the individual facts and circumstances.

191
192 The shorter the grace period, the more likely it is that the first company to obtain an approval
193 will have a period of de facto market exclusivity before other products obtain approval. For
194 example, if FDA provides a 1-year grace period before it takes action to remove unapproved
195 competitors from the market, and it takes 2 years for a second application to be approved, the
196 first approved product could have 1 year of market exclusivity before the onset of competition.
197 If the FDA provides for a shorter grace period, the period of effective exclusivity could be

⁸ These may be products that are the same as the approved product or a somewhat different product such as a different strength.

198 longer. The FDA hopes that this period of market exclusivity will provide an incentive to firms
199 to be the first to obtain approval to market a previously unapproved drug.⁹

⁹ The agency understands that, under the Act, holders of NDAs must list patents claiming the approved drug product and that newly approved drug products may, in certain circumstances, be eligible for marketing exclusivity. Listed patents and marketing exclusivity may delay the approval of competitor products. If FDA believes that an NDA holder is manipulating these statutory protections to inappropriately delay competition, the agency will provide relevant information on the matter to the Federal Trade Commission. In the past, FDA has provided information to the FTC regarding patent infringement lawsuits related to pending abbreviated new drug applications, citizen petitions, and scientific challenges to the approval of competitor drug products.

APPENDIX

BRIEF HISTORY OF FDA MARKETING APPROVAL REQUIREMENTS AND CATEGORIES OF DRUGS THAT LACK REQUIRED FDA APPROVAL¹⁰

Key events in the history of FDA's drug approval regulation and the categories of drugs affected by these events are described below.

A. 1938 and 1962 Legislation

The original Federal Food and Drugs Act of June 30, 1906, first brought drug regulation under federal law. That Act prohibited the sale of adulterated or misbranded drugs, but did not require that drugs be approved by FDA. In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act (the Act), which required that new drugs be approved for safety. As discussed below, the active ingredients of many drugs currently on the market were first introduced, at least in some form, before 1938. Between 1938 and 1962, if a drug obtained approval, FDA considered drugs that were identical, related, or similar (IRS) to the approved drug to be covered by that approval, and allowed those IRS drugs to be marketed without independent approval. Many manufacturers also introduced drugs onto the market between 1938 and 1962 based on their own conclusion that the products were generally recognized as safe (GRAS) or based on an opinion from FDA that the products were not new drugs. Between 1938 and 1962, the Agency issued many such opinions, although all were formally revoked in 1968 (see 21 CFR 310.100).

B. DESI

In 1962, Congress amended the Act to require that a *new drug* also be proven effective, as well as safe, to obtain FDA approval. This amendment also required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had approved as *safe* between 1938 and 1962 through the new drug approval process.

FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. The NAS/NRC created 30 panels of 6 professionals each to conduct the review, which was broken down into specific drug categories. The NAS/NRC reports for these drug products were submitted to FDA in the late 1960s and early 1970s. The Agency reviewed and re-evaluated the findings of each panel and published its findings in *Federal Register* notices. The FDA's administrative implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI). DESI covered the 3,400 products specifically reviewed by the NAS/NRCs as well as the even larger number of IRS products that entered the market without FDA approval.

Because DESI products were covered by approved (pre-1962) applications, the Agency concluded that, prior to removing products not found effective from the market, it would follow

¹⁰ This brief history document should be viewed as a secondary source. To determine the regulatory status of a particular category of drugs, the original source documents cited should be consulted.

244 procedures in the Act and regulations that apply when an approved new drug application is
245 withdrawn:

246

- 247 • All initial DESI determinations are published in the *Federal Register* and, if the drug is
248 found to be less than fully effective, there is an opportunity for a hearing.
- 249 • The Agency considers the basis of any hearing request and either grants the hearing or
250 denies the hearing on summary judgment and publishes its final determination in the
251 *Federal Register*.
- 252 • If FDA's final determination classifies the drug as effective for its labeled indications, as
253 required by the Act, the FDA still requires approved applications for continued marketing
254 of the drug and all drugs IRS to it.
- 255 • If FDA's final determination classifies the drug as ineffective, the drug and those IRS to it
256 can no longer be marketed and are subject to enforcement action.

257

258 1. Products Subject to Ongoing DESI Proceedings

259

260 Some unapproved marketed products are undergoing DESI reviews in which a final
261 determination regarding efficacy has not yet been made. In addition to the products specifically
262 reviewed by the NAS/NRC (i.e., those NDA'ed products approved for safety only between 1938
263 and 1962), this group includes unapproved products identical, related, or similar to those
264 products specifically reviewed (See 21 CFR 310.6). In virtually all these proceedings, the FDA
265 has made an initial determination that the products lack substantial evidence of effectiveness, and
266 the manufacturers have requested a hearing on that finding. It is the Agency's longstanding
267 policy that products subject to an ongoing DESI proceeding may remain on the market during
268 the pendency of the proceeding. See, e.g., *Upjohn Co. v. Finch*, 303 F. Supp. 241, 256-61 (W.D.
269 Mich. 1969).

270

271 2. Products Subject to Completed DESI Proceedings

272

273 Some unapproved marketed products are subject to already-completed DESI proceedings and
274 lack required approved applications. This includes a number of products IRS to DESI products
275 for which approval was withdrawn due to a lack of substantial evidence of effectiveness. This
276 group also includes a number of products IRS to those DESI products for which the FDA made a
277 final determination that the product is effective, but applications for the IRS products have not
278 been both submitted and approved as required under the statute and longstanding enforcement
279 policy (see 21 CFR 310.6). FDA considers all products described in this paragraph to be
280 marketed illegally.

281

282 **C. Prescription Drug Wrap-Up**

283

284 As mentioned above, many drugs came onto the market before 1962 without FDA approvals. Of
285 these, many claimed to be marketed prior to 1938 or IRS to such a drug. Drugs that did not have
286 pre-1962 approvals and were not IRS to drugs with pre-1962 approvals were not subject to
287 DESI. For a period of time, the FDA allowed these drugs to remain on the market and allowed

288 new unapproved drugs that were IRS to these pre-1962 drugs to enter the market without
289 approval.

290
291 Beginning in 1983, it was discovered that one drug that was IRS to a pre-1962 drug, a high
292 potency Vitamin E intravenous injection named E-Ferol, was associated with adverse reactions
293 in about 100 premature infants, 40 of whom died. In November of 1984, in response to this, a
294 congressional oversight committee issued a report to the FDA expressing the committee's
295 concern regarding the thousands of unapproved drug products in the marketplace.

296
297 In response to the E-Ferol tragedy, CDER assessed the number of pre-1962 non-DESI marketed
298 drug products. To address those drug products, the Agency significantly revised and expanded
299 CPG section 440.100 to cover all marketed unapproved prescription drugs, not just DESI
300 products. The program for addressing these marketed unapproved drugs and certain others like
301 them became known as the *Prescription Drug Wrap-Up*. Most of the Prescription Drug Wrap-
302 Up drugs first entered the market before 1938, at least in some form. For the most part, the
303 Agency had evaluated neither the safety nor the effectiveness of the drugs in the Prescription
304 Drug Wrap-Up.

305
306 Drugs that were subject to the Prescription Drug Wrap-Up are all marketed illegally, except in
307 the very unlikely circumstance that a manufacturer of such a drug can establish that its drug is
308 grandfathered or otherwise not a *new drug*.

309
310 Under the 1938 grandfather clause (see FDCA 201(p)(1), 21 U.S.C. 321(p)(1)), a drug product
311 that was on the market prior to passage of the 1938 Act and contained the same representations
312 concerning the conditions of use as it did prior to passage of that Act was not considered a *new*
313 *drug* and therefore was exempt from the requirement of having an approved new drug
314 application.

315
316 Under the 1962 grandfather clause, the Act exempts a drug from the effectiveness requirements
317 if its composition and labeling has not changed since 1962 and if, on the day before the 1962
318 Amendments became effective, it was (a) used or sold commercially in the United States, (b) not
319 a new drug as defined by the Act at that time, and (c) not covered by an effective application.
320 See Pub. L. 87-781, section 107 (reprinted following 21 U.S.C.A. 321); see also *USV*
321 *Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 662-66 (1973).

322
323 The two grandfather clauses in the Act have been construed very narrowly by the courts. The
324 FDA believes that there are few, if any, drugs on the market that are actually entitled to
325 grandfather status because the drugs currently on the market likely differ from the previous
326 versions in some respect, such as formulation, dosage or strength, method of manufacture,
327 dosage form, route of administration, indications, or intended patient population. See also the
328 changes described in 21 CFR 314.70(b). If a firm claims that its product is grandfathered, the
329 Agency considers it that firm's burden to prove that assertion (see 21 CFR 314.200(e)(5)).

330
331 Finally, a product may be not a *new drug* if it is generally recognized as safe and effective
332 (GRAS/GRAE) and has been used to a material extent and for a material time. See FDCA
333 201(p)(1) and (2), 21 U.S.C. 321(p)(1) and (2). As with the grandfather clauses, this has been
334 construed very narrowly by the courts. See, e.g., *Weinberger v. Hynson, Westcott & Dunning*,

335 *Inc.*, 412 U.S. 609 (1973); see also the Agency's April 26, 2001 decision in Docket No. 97N-
336 0314/CP2, finding that Synthroid (a levothyroxine sodium product) was not GRAS/GRAE.

337

338 As mentioned above, the Agency believes it is very unlikely that any currently marketed product
339 is grandfathered or is otherwise not a *new drug*. However, the Agency recognizes that it is at
340 least theoretically possible that such a product exists.

341

342 **D. New Unapproved Drugs**

343

344 Some unapproved drugs were first marketed (or changed) after 1962. These drugs are on the
345 market illegally. Some also may have already been the subject of a formal Agency finding that
346 they are new drugs. See, e.g., 21 CFR 310.502 (discussing, among other things, controlled/timed
347 release dosage forms).

348

349 **E. Over the Counter (OTC) Review**

350

351 Although OTC drugs were originally included in DESI, the FDA eventually concluded that this
352 was not an efficient use of resources. The Agency also was faced with resource challenges
353 because it was receiving many applications for different OTC drugs for the same indications.
354 Therefore, in 1972, the Agency implemented a process of reviewing OTC drugs through
355 rulemaking by therapeutic classes (e.g., antacids, antiperspirants, cold remedies). This process
356 involves convening an advisory panel for each therapeutic class to review data relating to claims
357 and active ingredients. These panel reports are then published in the *Federal Register*, and, after
358 FDA review, tentative final monographs for the classes of drugs are published. The final step is
359 the publication of a final monograph for each class, which sets forth the allowable claims,
360 labeling, and active ingredients for OTC drugs in each class (see, e.g., 21 CFR part 333). Drugs
361 marketed in accordance with a final monograph are considered to be generally recognized as safe
362 and effective (GRAS/GRAE) and do not require FDA approval of a marketing application.

363

364 Final monographs have been published for the majority of OTC drugs. Tentative final
365 monographs are in place for virtually all categories of OTC drugs. FDA has also finalized a
366 number of *negative monographs* that list therapeutic categories (e.g., topically applied hormones,
367 21 CFR 310.530) in which no OTC drugs can be marketed without approval. Finally, the
368 Agency has promulgated a list of active ingredients that cannot be used in certain unapproved
369 OTC drugs because there are inadequate data to establish that they are GRAS/GRAE (e.g.,
370 phenolphthalein in stimulant laxative products, 21 CFR 310.545(a)(12)(iv)(B)).

371

372 OTC drugs covered by ongoing OTC monograph proceedings may remain on the market as
373 provided in current enforcement policies (see, e.g., CPG section 450.200, 450.300, 21 CFR part
374 330). This document does not affect the current enforcement policies for such drugs.

375

376 OTC drugs that need approval because their ingredients or claims are not within the scope of the
377 OTC review or are not allowed under a final monograph or another final rule are illegally
378 marketed. For example, this group would include a product containing an ingredient determined
379 to be ineffective for a particular indication or one that exceeds the dosage limit established in the
380 monograph. Such products are new drugs that must be approved by FDA to be legally marketed.

381