



## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

#### **Termination of the Food and Drug Administration’s Unapproved Drugs Initiative; Request for Information Regarding Drugs Potentially Generally Recognized as Safe and Effective**

**AGENCY:** Food and Drug Administration (FDA), Department of Health and Human Services (HHS).

**ACTION:** Notice; request for information.

**SUMMARY:** The Department of Health and Human Services is issuing this Notice to withdraw FDA’s Marketed Unapproved Drugs – Compliance Policy Guide, Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs, and to request information from the public regarding drugs that may be grandfathered or generally recognized as safe and effective.

**DATES:** Part I of this Notice shall be effective thirty days from the date of publication in the **FEDERAL REGISTER**. To be considered, responses and comments related to Part II of this Notice must be received electronically at the email address listed below. The Department will consider information submitted by the public in response to Part II of this Notice on a rolling basis, and until further notice.

**ADDRESSES:** Responses to Part II must be submitted electronically, and should be addressed to [Import@hhs.gov](mailto:Import@hhs.gov). In the subject line of the email message, submissions should include “GRASE RFI Response.”

**FOR FURTHER INFORMATION CONTACT:** Nick Uehlecke, 200 Independence Ave SW, Washington, DC 20201; or by email at [Import@hhs.gov](mailto:Import@hhs.gov); or by telephone at 1–877–696–6775.

**SUPPLEMENTARY INFORMATION:** The Trump Administration, through the Department of Health and Human Services (HHS), is continuing its efforts to reduce the price of prescription drugs. This Notice addresses two related but distinct issues: (1) the Food and Drug Administration’s (FDA) Unapproved Drugs Initiative (UDI) and (2) the construction of the

statutory exemptions from the definition of “new drugs” subject to FDA approval under the federal Food, Drug, and Cosmetic Act (FD&C Act), namely so-called pre-1938 grandfathered drugs and drugs that are “generally recognized as safe and effective” or “GRASE.”

## **I. Unapproved Drugs Initiative**

In 1938, Congress created the modern scheme for federal regulation of drugs. Before 1938, there was no requirement under federal law for a manufacturer to obtain FDA approval before marketing a drug. Today, as a general rule, under the FD&C Act, a “new drug” must be approved by the FDA for safety and efficacy pursuant to an approved New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) before the drug is introduced into interstate commerce. *See* FD&C Act 201(p), 21 U.S.C. 321(p) (defining “new drug” under the Act); FD&C Act 505(a), 21 U.S.C. 355(a) (“No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug.”). A “person” that introduces a “new drug” into interstate commerce is subject to, among other sanctions, injunctions and/or having the subject product seized in an ex parte proceeding under admiralty rules. *See* FD&C Act 302, 21 U.S.C. 332 (injunction authority); FD&C Act 304, 21 U.S.C. 334 (seizure authority).

Not all drugs are “new drugs” which require FDA approval. There are two primary carve-outs from the FD&C Act’s definition of “new drug.”<sup>1</sup> First, when Congress enacted the modern FD&C Act in 1938, it exempted from the definition of “new drug” all drugs “subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use.” FD&C Act 201(p)(1), 21 U.S.C.

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<sup>1</sup> There is a third, related exemption which relieves manufacturers from the obligation of showing their drugs are effective prior to marketing. In section 107(c)(4) of the Drug Amendments of 1962, Pub. L. No. 87-81, 76 Stat. 780, 789 (Oct. 10, 1962), Congress exempted from the efficacy requirement “product[s] that, on the day before the 1962 amendments became effective, (A) [were] used or sold commercially in the United States, (B) [were] generally recognized by the experts as safe; and (C) [were] not ‘covered’ by an ‘effective’ application.” *USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 653 (1973). In *Weinberger*, the Supreme Court held that so-called “me-too drugs,” i.e., drugs that were copies of NDA drugs, were effectively “covered” by an effective application and thus subject to the efficacy requirement just like drugs covered by NDAs. *Id.* at 664-65. Practically, *Weinberger* left as the lone remaining candidates for this exemption from the efficacy requirement drugs (a) on the market prior to 1962, (b) generally recognized as safe, and (c) not themselves subject to a 1938-1962 “effective” NDA.

321(p)(1). Second, drugs that are generally recognized as safe and effective which have also “been used to a material extent or for a material time” are not “new drugs.” FD&C Act 201(p)(1) and (2), 21 U.S.C. 321(p)(1) and (2). Drugs that meet either of these exceptions may be legally marketed without FDA pre-approval for safety and efficacy, subject to the agency’s other regulatory authorities.

Through a guidance document issued in 2006 and later revised in 2011, and without conducting notice-and-comment rulemaking, FDA launched a program called the Unapproved Drugs Initiative (UDI).<sup>2</sup> The UDI sprang from a laudable objective, namely to reduce the number of unapproved drugs on the market. To achieve this end, FDA provided in its 2011 UDI Guidance that “the first company to obtain an approval [of a previously unapproved drug] will have a period of de facto market exclusivity before other products obtain approval.”<sup>3</sup> The agency “hope[d] that this period of market exclusivity will provide an incentive to firms to be the first to obtain approval to market a previously unapproved drug.”<sup>4</sup> Ultimately, manufacturers of older drugs previously thought to be exempt from the FDA approval requirement obtained market exclusivity for those products after FDA took unapproved versions off the market. An unintended consequence of the “period of de facto market exclusivity” provided by the UDI allowed manufacturers an opportunity to raise prices in an environment largely insulated from market competition.

Based on its ongoing review of FDA regulatory programs, the Department has decided to withdraw the 2006 and 2011 Guidance, effective thirty days after the date of publication of this Notice in the **Federal Register**. All compliance manuals, website statements, and other informal issuances with respect to the 2006 and 2011 Guidance are also hereby withdrawn. The withdrawal of the 2006 and 2011 Guidance Documents complies with FDA’s current Good

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<sup>2</sup> FDA, *Marketed Unapproved Drugs — Compliance Policy Guide Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs* (June 2006) (hereinafter the 2006 Guidance); FDA, *Marketed Unapproved Drugs — Compliance Policy Guide Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs* (Sept. 19, 2011) (hereinafter the 2011 Guidance).

<sup>3</sup> 2011 Guidance at 8.

<sup>4</sup> *Id.*

Guidance Practices regulation, which allows for “periodic[] review of [of] existing guidance documents to determine whether they need to be changed or withdrawn.” 21 C.F.R.

10.115(k)(1). Nothing in this Notice otherwise limits FDA’s authority to take action against manufacturers of unapproved drugs that meet the statutory definition of a “new drug” (such as, for example, an unapproved drug that claims to mitigate, treat, or cure COVID-19) or violate the FD&C Act in other ways. Further, nothing in this Notice limits FDA’s grant of regulatory exclusivities authorized by statute, such as a new chemical entity exclusivity, orphan drug exclusivity, or pediatric exclusivity. This Notice does not apply to drugs subject to (1) Investigational New Drug applications (IND) that are in effect as of the effective date of this Notice, (2) any subsequent NDA based on new clinical trial investigations (other than bioavailability studies) derived under such IND, and (3) existing approved NDAs.

The Department is withdrawing the 2006 and 2011 Guidances for several evidence-based reasons. After the UDI began, reports emerged that Americans were paying significantly more for prescription drugs approved by FDA through the UDI than they had paid previously. One report noted that a drug approved through the UDI “sells for about \$4.50 a tablet—nearly 50 times the price of the unapproved version.”<sup>5</sup> Another report asserted that “[t]hanks at least partially to the FDA program, the price of vasopressin . . . has risen 10-fold” and the cost of “a vial of neostigimine . . . has gone from less than \$5 to \$90.”<sup>6</sup>

In 2017, scholars from the Yale School of Medicine and the University of Utah published a peer-reviewed study corroborating the previous reports.<sup>7</sup> The study reviewed 34 drugs subject to the UDI between 2006 and 2015. The scholars found the average wholesale unit price of 26 of the 34 drugs for which pricing data was available increased by a median of 37% (interquartile

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<sup>5</sup> Harris Meyer, *The High Price of FDA Approval*, KAISER HEALTH NEWS, Dec. 29, 2009, <https://khn.org/news/fda-approval/>.

<sup>6</sup> Michael Hiltzik, *The little-known FDA program that’s driving drug prices higher*, L.A. TIMES (Sept. 23, 2015), <https://www.latimes.com/business/hiltzik/la-fi-mh-the-little-known-fda-program-20150923-column.html>.

<sup>7</sup> Ravi Gupta et al., *The FDA Unapproved Drugs Initiative: An Observational Study of the Consequences for Drug Prices and Shortages in the United States*, 23 J. OF MAN. CARE & SPECIALTY PHARM. 1066 (Oct. 2017).

range of 23%-204%).<sup>8</sup> The average wholesale unit price of 11 of the drugs surveyed in the study increased by more than 128%.<sup>9</sup>

The study also linked the UDI to drug shortages, which the authors defined as “a supply issue that affects how a pharmacy prepares or dispenses a drug product that influences patient care when prescribers must use an alternative agent.”<sup>10</sup> In this regard, the scholars found that 24 of the 34 drugs experienced shortages after FDA took enforcement action after an entity obtained FDA approval of a previously unapproved drug. The median shortage was 217 days.<sup>11</sup>

Finally, the authors considered whether the UDI generated new clinical data evidence for older drugs. The authors found that, of the nineteen drugs that obtained FDA approval during the study period, only two were supported by “new clinical trial evidence.”<sup>12</sup> The other seventeen drugs “were supported by literature reviews and bioequivalence to older drug products.”<sup>13</sup>

Therefore, the Department has concluded that while the UDI began with laudable goals, it has had numerous negative, unintended consequences on Americans’ access to prescription drugs and generated very limited benefits.

Moreover, the fact that the program was initiated through guidance, as opposed to notice-and-comment rulemaking, further supports the Department’s decision to withdraw the 2006 and 2011 Guidances, because the Department has serious legal concerns about whether the UDI was implemented through legally permissible procedures.<sup>14</sup> The Department recognizes that some

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<sup>8</sup> *Id.* at 1071.

<sup>9</sup> *See id.* at 1072.

<sup>10</sup> *Id.* at 1068.

<sup>11</sup> *Id.* at 1073.

<sup>12</sup> *Id.*

<sup>13</sup> *Id.*; *see also* Aaron S. Kesselheim and Daniel H. Solomon, *Incentives for Drug Development – The Curious Case of Colchicine*, N. ENGL. J. MED. 362;22 at 2046 (noting the dramatic rise in the price of Colchicine after implementation of the UDI, but that “there is no evidence of any meaningful improvement to the public health” from the regulatory changes).

<sup>13</sup> 36 FR 14662, 14662-63 (Aug. 7, 1971).

<sup>14</sup> *See, e.g.*, 5 U.S.C. 553. The Department also has concerns regarding whether the issuance of the 2011 Guidance complied with FDA’s good guidance practices regulation, 21 C.F.R. 10.115, in effect at the time. FDA issued the 2011 Guidance “without public comment because the Agency has determined that prior public participation is not feasible or appropriate.” 76 FR 58398 (Sept. 21, 2011).

persons might contend that they have reliance interests in the 2011 Guidance remaining in effect. In *Dep't of Homeland Sec. v. Regents of the Univ. of California*, 140 S. Ct. 1891 (2020), the Supreme Court struck down the Department of Homeland Security's rescission of the Deferred Action for Childhood Arrivals (DACA) immigration program, in part based on the reliance interests of persons eligible to obtain the benefits of the program. Notably, in that case, immigration authorities "solicited applications from eligible aliens, instituted a standardized review process, and sent formal notices indicating whether the alien would receive the two-year forbearance." *Id.* As the Court explained, DACA "created a program for conferring affirmative immigration relief." *Id.*

The UDI is distinguishable from the DACA program. Unlike DACA, the 2011 Guidance described how the FDA intended to exercise its enforcement discretion, but stopped short of committing FDA to any particular action. FDA stated that it was "more likely to take enforcement action" against unapproved competitors of newly approved drugs under the UDI, but that the agency "intend[s] to take into account the circumstances once the product is approved in determining how to exercise our enforcement discretion with regard to the unapproved products."<sup>15</sup> Moreover, the 2011 Guidance stated that it "does not create or confer any rights for or on any person and does not operate to bind FDA or the public."<sup>16</sup> Any reliance interests are thus illusory. Furthermore, Congress vested FDA with the sole authority to enforce the FD&C Act. FD&C Act 310, 21 U.S.C. 337. Under *Heckler v. Chaney*, 470 U.S. 821 (1985), FDA's decision about the extent to which it shall enforce the FD&C Act is unreviewable under the Administrative Procedure Act.

Even if there were cognizable reliance interests in the UDI, the Department has ample evidence-based justification for rescinding the 2006 and 2011 Guidances. After more than fourteen years of experience with the program, evidence has emerged that the UDI has caused

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<sup>15</sup> 2011 Guidance at 7.

<sup>16</sup> *Id.* at 2.

significant prescription drug price increases and drug shortages while providing limited new clinical data on older drugs. The Department believes these costs imposed on American patients and taxpayers outweigh any reliance interests that may exist in the program. The Department has also considered the public health effects of withdrawing the 2006 and 2011 Guidances. As the 2011 Guidance acknowledges, there are “several thousand” products on the market that lack FDA approval.<sup>17</sup> To the extent this program has limited patient access to important, safe medications due to price increases or drug shortages, the withdrawal of the 2006 and 2011 Guidances will have a positive impact on public health. Moreover, eliminating this program allows FDA’s resources to be directed toward monitoring unapproved “new drugs” that fall squarely within the traditional scope of the definition of that term in the FD&C Act. At the same time, the Notice allows FDA to use its limited review resources on innovative potential therapies, as opposed to older drugs with longstanding use.

Besides, any reliance interests (if they existed) would be minimal. This Notice does not apply to drugs subject to (1) INDs in effect as of the effective date of this Notice, (2) any subsequent NDA based on new clinical investigations (other than bioavailability studies) derived under such IND, and (3) existing approved NDAs.

## **II. Pre-1938 Grandfathered and GRASE Drugs; Request for Information**

As noted above, when Congress enacted the FD&C Act in 1938 and later amended the Act in 1962, it exempted certain drugs from the FDA approval requirement. Section 201(p) of the FD&C Act, 21 U.S.C. 321(p), excludes from the definition of “new drug” certain drugs marketed prior to June 25, 1938 and drugs generally recognized as safe and effective, or GRASE. In the 2011 Guidance, FDA stated that “it is not likely that any currently marketed prescription drug is grandfathered or is otherwise not a *new drug*,” though the agency stated “that it is at least theoretically possible.”<sup>18</sup>

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<sup>17</sup> *Id.* at 3.

<sup>18</sup> *Id.* at 12 (emphasis in original).

That was not always the case. For many years, FDA acknowledged that at least some drugs are not “new drugs” subject to FDA approval prior to marketing. In a 1980 version of the *Orange Book*, FDA stated that “[t]he law also permits drugs to be legally marketed without such fully approved applications under certain circumstances,” including “drugs marketed prior to 1938 that are not subject to the pre-market clearance procedures of the law” and “drug products marketed between 1938 and 1962 that were approved for safety but not effectiveness.”<sup>19</sup> In the same publication, the agency went on to identify specific products, noting “commonly used large volume intravenous products are not included on the List [of FDA-approved drugs] (e.g., dextrose 5% with water, dextrose 10% with water, sodium chloride 0.9% injection),” since “all of these drug products came on the market in glass containers before 1938 and have not been required to obtain an approved new drug application as a condition of marketing.”<sup>20</sup> In the 2000 edition of the *Orange Book*, FDA cited to the barbiturate “Phenobarbital Tablets” as an example of “pre-1938 drugs.”<sup>21</sup> The 2011 Guidance, issued absent notice-and-comment rulemaking and without prior public comment, contains no acknowledgement of these prior positions.<sup>22</sup>

This evolution in the agency’s thinking has had consequences. Under the UDI, FDA required the manufacturer of an epinephrine brand which originally came onto the market in 1901 to submit an NDA.<sup>23</sup> The drug colchicine, a product FDA acknowledged “was available in oral dosage form during the 19th century,”<sup>24</sup> was also approved through the UDI. The interpretation of the definition of “new drug” espoused in the 2011 Guidance essentially

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<sup>19</sup> FDA, *Approved Prescription Drug Products with Therapeutic Equivalence Evaluations* (herein the *Orange Book*), at I-3 (1st ed. 1980).

<sup>20</sup> *Id.* at I-13.

<sup>21</sup> *Id.* at I-13. FDA, *Orange Book*, at v (2000); see also FDA, *Orange Book*, at iv (29th ed. 2009) (containing same reference to “pre-1938 drugs” and phenobarbital tablets). FDA included a reference to “pre-1938 drugs” like phenobarbital tablets in the *Orange Book* as late as 2016, FDA, *Orange Book*, at iv (36th ed. 2016), but removed the reference in its 2017 edition and subsequent versions.

<sup>22</sup> *Cf. F.C.C. v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009) (“To be sure, the requirement that an agency provide reasoned explanation for its action would ordinarily demand that it display awareness that it *is* changing position.”)

<sup>23</sup> FDA, Ctr. For Drug Evaluation and Research, Application Number: 204200Orig1s000, 204200Orig2s000, Summary Review, at 3, [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/204200Orig1Orig2s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/204200Orig1Orig2s000SumR.pdf).

<sup>24</sup> 75 FR 60768 (Oct. 1, 2010).

foreclosed the possibility that these two century-old drugs were pre-1938 grandfathered drugs exempt from the approval process. The 2017 study discussed above found that the average wholesale unit price of epinephrine and colchicine increased by 58.3% and 3,323.5%, respectively,<sup>25</sup> costs absorbed by American patients and taxpayers.

The regulatory history of the prescription drug Daraprim raises similar issues. FDA originally approved Daraprim (pyrimethamine) for safety in 1953, and later deemed the drug effective through the Drug Efficacy Study Implementation, or DESI review process.<sup>26</sup> The drug is listed on the World Health Organization’s *List of Essential Medications*, “a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions.”<sup>27</sup> In 2015, the company Turing Pharmaceuticals “raised the price [of the drug] to \$750 a tablet from \$13.50, bringing the annual cost of treatment for some patients to hundreds of thousands of dollars.”<sup>28</sup> Turing came by this windfall, at least in part, because of FDA’s interpretation of the definition of “new drug” in the FD&C Act as articulated in the 2006 and 2011 Guidances, a view that foreclosed the possibility that Daraprim, a drug more than sixty years old, could ever qualify as GRASE. That position effectively prevented other manufacturers of generic versions of this product from entering the market without an approved abbreviated new drug application, allowing Turing to enjoy a single-source position in the marketplace while potential competitors went through the regulatory process. In February 2016, Congress held a hearing on this widely-publicized issue. Ultimately, FDA approved a generic competitor for this single-source drug in February 2020.

The Department wishes to engage with the public on the contours of the exceptions to the definition of “new drug.” In this regard, HHS is reviewing whether certain drugs, including the

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<sup>25</sup> Gupta, *supra* note 7, at 1072; *see also* Aaron S. Kesselheim and Daniel H. Solomon, *Incentives for Drug Development – The Curious Case of Colchicine*, N. ENGL. J. MED. 362:22 at 2046 (noting the dramatic rise in the price of Colchicine after implementation of the UDI, but that “there is no evidence of any meaningful improvement to the public health” from the regulatory changes).

<sup>26</sup> 36 FR 14662, 14662-63 (Aug. 7, 1971).

<sup>27</sup> World Health Organization, *20th WHO Model List of Essential Medications*, at 24 (Mar. 2017).

<sup>28</sup> Andrew Pollack, *Drug Goes From \$13.50 a Tablet to \$750, Overnight*, N.Y. TIMES, Sept. 20, 2015, <https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html>.

drug subject to Congressional scrutiny in 2016, might qualify as exempt from the FDA approval requirement. To aid that effort, HHS asks for input from patients, health care providers, industry, and other stakeholders to provide information responsive to any of the topics below:

1. Lists of drugs marketed prior to June 25, 1938 that are currently available on the market.
2. The extent to which drugs marketed prior to June 25, 1938, or drugs that might qualify as GRASE, have regulatory approvals in countries outside the United States.
3. Whether there would be adverse clinical or economic consequences to deeming as GRASE those drugs previously approved by the FDA for which patent and regulatory exclusivity have expired.
4. Any published literature reviews or clinical studies related to any drugs potentially exempt from the new drug approval requirement.

Dated: November 20, 2020.

**Alex M. Azar II,**

*Secretary,*

*Department of Health and Human Services.*