4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2020-Z-2200]

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

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

ACTION: Notice; withdrawal.

SUMMARY: The Department of Health and Human Services (HHS or the Department) is issuing this document to withdraw a legally and factually inaccurate notice and request for information published in the *Federal Register* on November 25, 2020, entitled "Termination of the Food and Drug Administration's Unapproved Drugs Initiative; Request for Information Regarding Drugs Potentially Generally Recognized as Safe and Effective." This notice also ends the period for submission of responses to Part II of the November 25, 2020, notice and request for information.

DATES: The notice and the request for information are withdrawn as of **[INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].**

FOR FURTHER INFORMATION CONTACT: Anuj Shah, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6224, Silver Spring, MD 20993, 301-796-2246.

SUPPLEMENTARY INFORMATION: On November 25, 2020, HHS published a notice and a request for information in the *Federal Register* entitled "Termination of the Food and Drug Administration's Unapproved Drugs Initiative; Request for Information Regarding Drugs Potentially Generally Recognized as Safe and Effective" (the HHS Notice) (85 FR 75331). The

HHS Notice stated that it was "terminating" the FDA's Unapproved Drugs Initiative (UDI) effective 30 days from publication of the HHS Notice in the *Federal Register*, by withdrawing FDA's "Marketed Unapproved Drugs Compliance Policy Guide" (CPG 440.100). The HHS Notice also requested public input on four topics that relate to the statutory exemptions from the definition of "new drug" in the Federal Food, Drug, and Cosmetic Act (FD&C Act). The request for responses stated that: "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." The responses were directed to be submitted to an HHS email address with a specific subject line.

Because the HHS Notice contained multiple legal and factual inaccuracies, it is hereby withdrawn. Further, no responses or information submitted to the HHS email Import@hhs.gov, in response to the HHS Notice and request for information, on or after **[INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]** will be considered by HHS or FDA. All website statements and other informal issuances with respect to the HHS Notice are also hereby withdrawn. The HHS Notice withdrew FDA's guidance CPG 440.100, but that withdrawal does not represent a change in the legal obligations that apply to new drugs or to FDA's existing enforcement authority over unapproved new drugs.

Central to the legal and factual inaccuracies in the HHS Notice is its misinterpretation of the term "new drug." The definition of "drug" in section 201(g)(1) of the FD&C Act (21 U.S.C. 321(g)(1)) includes articles intended for use in the "diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals"; "articles (other than food) intended to affect the structure or any function of the body of man or other animals"; and articles "intended for use as a component" of the foregoing articles. A drug is a "new drug," and is generally subject to the requirements for "new drugs," unless the drug is generally recognized by qualified experts as safe and effective (GRASE) for its labeled uses and used to a material extent or for a material time or the drug is grandfathered because it was marketed before 1938 (section 201(p) of the FD&C Act). A separate "grandfather" clause exempts a drug from the "effectiveness"

requirements if, before 1962, the drug was: (1) used or sold commercially in the United States; (2) not a "new drug" as defined by the FD&C Act at that time; and (3) not covered by an effective application. Under section 505(a) of the FD&C Act (21 U.S.C. 355(a)), before any "new drug" may be legally marketed in the United States, it must be the subject of an approved application submitted pursuant to section 505(b) or section 505(j) of the FD&C Act, unless an exception applies. A biological product (defined in section 351(i) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(i)) with an approved license under section 351 of the PHS Act is not required to have an approved application under section 505 of the FD&C Act.

For decades, FDA has interpreted the word "drug" in the term "new drug" to refer to the entire drug product and not just its active ingredient. This interpretation has significant implications for public health. An active ingredient can have different effects on the body depending on the formulation of the drug and its route of administration (e.g., topical vs. intravenous), among other things.[1] That is why when it reviews an application, FDA carefully evaluates, for each drug product, not only the active ingredient but also information about the drug's formulation, route of administration, labeling, inactive ingredients, bioavailability, and manufacturing processes. In accordance with this approach, FDA has consistently argued in the courts that the term "drug" in "new drug" means the entire drug product and not only an active ingredient, and courts, including the U.S. Supreme Court, have agreed with FDA's interpretation. See *U.S.* v. *Generix Drug Corp*., 460 U.S. 453, 458-59 (1983) (the FD&C Act's definition of "new drug" applies to the entire drug product rather than the active ingredient); see also *U.S.* v.

[1] For example, Elixir Sulfanilamide, a liquid version of sulfanilamide (an early antibiotic widely used in the 1930s and 1940s to treat streptococcal infections), was responsible for the deaths of more than 100 people in 1937. The liquid formulation was manufactured using sulfanilamide as the active ingredient in a diethylene glycol-based solution. Had the manufacturer conducted an animal study or a review of then-existing scientific journals, it would have revealed the highly toxic nature of the inactive ingredient diethylene glycol, but Federal law at the time did not require such studies, nor did it require premarket review of the drug by FDA. This tragedy spurred Congress to enact the FD&C Act in 1938, which required that new drugs be approved by FDA for safety before they could be marketed. Another example occurred in 1983, when 38 premature infants died and 43 were seriously injured after being intravenously administered E-Ferol, an unapproved high potency form of vitamin E. Injectable vitamin E drugs for use in premature infants had been marketed since at least 1949; however, E-Ferol was a new formulation, containing higher levels of vitamin E and using a relatively high concentration of two polysorbates as emulsifiers, which subsequent research suggests were likely responsible for the injuries and deaths of the premature infants.

Premo Pharmaceutical Lab., 629 F.2d 785 (2d Cir. 1980). FDA regulations incorporate FDA's interpretation of "new drug" (see 21 CFR 314.200), and a product-specific interpretation of "new drug" underpins FDA's drug regulatory system.

FDA has long employed a risk-based enforcement approach with respect to new drugs marketed without an approved application. In October 2003, the Agency published a draft guidance, entitled "Marketed Unapproved Drugs--Compliance Policy Guide," to clarify how FDA generally intended to exercise its enforcement discretion regarding illegally marketed unapproved new drugs (October 23, 2003, 68 FR 60702). In June 2006, FDA finalized the 2003 draft guidance in a final guidance entitled "Marketed Unapproved Drugs--Compliance Policy Guide Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs" (CPG 440.100 guidance) (June 9, 2006, 71 FR 33466). The CPG 440.100 guidance described how FDA intended to prioritize regulatory action under its existing enforcement authority regarding currently marketed unapproved new drugs, including that FDA generally intended to apply a risk-based approach.

In 2011, FDA updated the CPG 440.100 guidance to clarify that unapproved new drugs introduced onto the market after September 19, 2011, were subject to enforcement action at any time without regard to the enforcement priorities set out in CPG 440.100 (September 21, 2011, 76 FR 58398). As described in the updated version of the CPG 440.100 guidance, FDA generally intended to encourage manufacturers of unapproved new drugs to submit applications for their products, while continuing to apply a risk-based approach to removing unapproved new drugs from the market and preserving access to medically necessary drugs.

The CPG 440.100 guidance was part of FDA's UDI, which focuses on addressing the continued illegal marketing in the United States of drug products that lack the required FDA review and approval for safety and efficacy. To address this problem, FDA's UDI adopts a risk-based approach for removing from the market unapproved new drugs, particularly those that pose serious risks to patients, with the goal of also preserving patient access to medically

necessary drugs and encouraging manufacturers of unapproved new drugs to submit applications for their products. The UDI has a two-pronged approach to help assure patient safety. First, the Agency encourages manufacturers of unapproved new drugs to obtain approval to be legally marketed in the United States. Second, FDA works to remove unapproved new drugs from the market consistent with risk-based enforcement priorities and existing enforcement authorities.

As a result of the UDI, FDA has initiated 45 actions since 2006 (some affecting multiple unapproved new drugs) that have led to hundreds of potentially unsafe drugs being voluntarily removed from the market, including several drugs with significant safety concerns. These drugs were removed from the market in response to FDA *Federal Register* notices announcing that FDA intended to take enforcement action (13 of the actions), warning letters (15 of the actions), or at FDA's informal request through communications such as a teleconference (17 of the actions). In all 45 actions, safety concerns supported removal of the unapproved new drug products from the market, such as serious adverse events, labeling that did not adequately warn healthcare professionals of risks, or potential risks of harm resulting from adulterated drugs produced by facilities with current good manufacturing practice violations.

The following are well-documented examples of significant adverse events associated with unapproved new drugs that resulted in compliance actions to remove an entire class of unapproved new drugs from the market. As noted below, these compliance actions have also spurred manufacturers to seek and obtain FDA approval of safe and effective versions of these drugs:

- *Carbinoxamine-containing products*
    - Between 1983 and 2006, FDA became aware of 21 deaths in children under 2 years of age associated with the use of carbinoxamine-containing drugs, including unapproved drugs. FDA had concerns about the risks associated with these products because, although their safety and effectiveness had not been studied in infants and young children, they were promoted for use in this vulnerable age group. As a result,

in June 2006, FDA issued a *Federal Register* notice announcing that it intended to take enforcement action against unapproved drug products containing carbinoxamine and those who cause the manufacture of such products.[2] As of February 2021, six FDA-approved carbinoxamine-containing drug products, including five generic versions, are available on the marketplace and are labeled as contraindicated in children under 2 years old.

- *Quinine*
  - Between 1969 and 2006, FDA received 665 adverse events reports, including 93 deaths, associated with unapproved quinine sulfate use. Among the more common types of events with serious outcomes reported to the Agency were cardiac events, renal failure, and events related to overdose. FDA approved its first quinine sulfate product in August 2005, and the approved labeling for quinine sulfate provides extensive warnings to ensure its safe use. After a safe and effective FDA-approved quinine sulfate product became available, in December 2006, FDA issued a *Federal Register* notice announcing that it intended to take enforcement action against unapproved drug products containing quinine (including quinine sulfate and other salts of quinine) and persons who cause the manufacture of such products or their shipment in interstate commerce because these products presented serious safety risks that the unapproved drug labeling did not comprehensively describe.[3] As of February 2021, there are five FDA-approved quinine sulfate capsules, including four generic drug products, available in the marketplace.

As noted above, these compliance actions have resulted in potentially unsafe unapproved new drugs being removed from the market as well as FDA approval of safe and effective versions of drug products previously marketed without approval. Approval of formerly

[2] 71 FR 33462 (June 9, 2006). See https://www.govinfo.gov/content/pkg/FR-2006-06-09/pdf/E6-9033.pdf.
[3] 71 FR 75557 (December 15, 2006). See https://www.govinfo.gov/content/pkg/FR-2006-12-15/pdf/06-9713.pdf.

unapproved new drugs helps reduce concerns about a potential market disruption or shortage of these drugs, because the manufacturers of approved drugs have invested in a manufacturing process that helps to ensure the drug is produced reliably and consistently. This lowers the risk of quality problems, which are one of the main causes of shortages.[4] In addition, the approval of previously unapproved new drugs assures the American public that the approved versions of those drugs are safe and effective for their intended uses, manufactured in accordance with Federal quality standards, and bear accurate and complete information in their labeling regarding risks, benefits, and safe use.

On November 25, 2020, HHS published the HHS Notice in the *Federal Register* stating that it was "terminating" the UDI by withdrawing FDA's CPG 440.100 guidance, effective 30 days from the publication date. HHS also issued a request for information regarding the definition of "new drug" under section 201(p) of the FD&C Act and whether certain drugs might be grandfathered or qualify as GRASE and therefore would not be subject to the new drug approval requirement. We did not find any evidence that HHS consulted with, otherwise involved, or even notified FDA before issuing the HHS Notice. Section 1003(d) of the FD&C Act (21 U.S.C. 393(d)) provides that the Secretary "shall be responsible for executing" the FD&C Act "through the [FDA] Commissioner." Here, the HHS Notice in withdrawing the CPG 440.100 guidance is clearly an action "executing" the FD&C Act.

The HHS Notice misinterprets the statutory term "new drug." First, the HHS Notice erroneously suggests that FDA has taken the position that drug substances (i.e., active ingredients) marketed prior to June 25, 1938, could be "grandfathered" under the statute, and therefore, are not "new drugs" subject to FDA's new drug approval process. As explained above, FDA has long interpreted the word "drug" in "new drug" to refer to the entire drug product and not just the active ingredient, and the U.S. Supreme Court has ruled that this is the

[4] FDA, Drug Shortages: Root Causes and Potential Solutions (2019), available at https://www.fda.gov/media/131130/download.

correct interpretation of that term. Consistent with this product-specific interpretation of "new drug," FDA has construed the grandfather clause in section 201(p)(1) of the FD&C Act to mean that a drug product cannot be grandfathered if it differs in any respect from the pre-1938 version of the drug product. Second, the HHS Notice erroneously suggests that FDA had interpreted the definition of "new drug" to exclude drug products with active ingredients marketed prior to June 25, 1938, but that FDA failed to acknowledge this interpretation in the CPG 440.100 guidance, as part of the UDI. In fact, the CPG 440.100 guidance did not change FDA's interpretation of "new drug;" the CPG reflected the interpretation that the Agency had applied for decades and that was upheld by the U.S. Supreme Court in 1983.

The HHS Notice also includes other misstatements, including erroneously describing the UDI and FDA's CPG 440.100 guidance as a new policy that should have been adopted through notice-and-comment rulemaking. However, the CPG 440.100 guidance did not change FDA's interpretation of "new drug," "grandfathered," or "GRASE." Instead, it described FDA's enforcement priorities under FDA's existing legal authorities regarding illegally marketed unapproved new drugs. Communicating enforcement policies through guidance documents rather than legislative rules is consistent with both the Administrative Procedure Act (APA; 5 U.S.C. 551 *et seq*.) and FDA's regulations on good guidance practices (§ 10.115 (21 CFR 10.115)). Under the APA, FDA may use guidance documents to "advise the public prospectively of the manner in which the agency proposes to exercise a discretionary power."[5] Accordingly, FDA's good guidance practice regulations define "guidance documents" to include "documents that relate to…enforcement policies." (§ 10.115(b)(2)).

Additionally, the HHS Notice is supported by flawed facts. It cites, for the proposition that the UDI and CPG 440.100 guidance resulted in price increases for certain new drugs, only a single observational study of 26 products, which included pricing estimates that were not inflation-adjusted over the 4-year observational period, which could lead to an overestimation of

[5] See the Attorney General's Manual on the APA (1947), at 30 n.3.

real price changes.[6] The HHS Notice also erroneously ties the 2015 price increase for the drug DARAPRIM to the UDI. DARAPRIM was approved as a new drug under the FD&C Act in 1953. Following the 1962 FD&C Act amendments, which required drugs to demonstrate not only safety but efficacy, DARAPRIM was found to be effective, in 1971, as part of FDA's review of all new drugs that had been approved only for safety before 1962. DARAPRIM was then fully approved by FDA as a safe and effective drug. For years after its approval, DARAPRIM was an off-patent, off-exclusivity drug eligible for generic competition, but no drug manufacturer sought and obtained approval of a generic version during this period. It was during this period, in 2015, that the holder of the approved application for DARAPRIM significantly raised the price of the drug. FDA recently approved a generic version of this product on February 28, 2020.[7]

Due to the HHS Notice's legal and factual inaccuracies, including those described above, HHS and FDA believe it is appropriate to withdraw the HHS Notice at this time. The HHS Notice does not accurately reflect the Department's or FDA's thinking because it is inconsistent with the FD&C Act, FDA regulations, and judicial precedent, among other legal authorities, and is not supported by the facts. In addition, the HHS Notice could result in significant harm to public health by suggesting that unsafe or ineffective drugs could circumvent the drug approval process.

Although the withdrawal of FDA's CPG 440.100 guidance does not change the legal obligations that apply to new drugs, or FDA's existing enforcement authority over unapproved new drugs, we recognize that the withdrawal of the CPG may have created confusion for the

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[6] See R. Gupta et al., "The FDA Unapproved Drugs Initiative: An Observational Study of the Consequences for Drug Prices and Shortages in the United States," 23 *Journal of Managed Care & Specialty Pharmacy* 1066 (October 2017) (the Yale Study). Of note, the authors of the Yale Study suggested ways to mitigate unintended consequences of the UDI that did not include terminating the UDI by withdrawing CPG 440.100 guidance or reinterpreting the definition of "new drug."

[7] FDA continues to maintain efforts to improve the efficiency of the generic drug development, review, and approval process, generally, and it prioritizes the review of submissions for generic drugs for which there are fewer than three approved generic versions for the reference listed drug (RLD) and for which there are no blocking patents or exclusivities on the RLD.

public, including regulated industry, as to how FDA intends to prioritize its enforcement resources in this area. FDA therefore plans to issue guidance on this topic consistent with good guidance practices. The guidance will provide appropriate updates regarding FDA's enforcement priorities for marketed unapproved new drugs. In the interim, before such guidance is issued, FDA will continue to exercise its existing general approach to prioritizing regulatory and enforcement action, which involves risk-based prioritization in light of all the facts of a given circumstance. Risk-based enforcement best supports FDA's public health priorities.

FDA's longstanding interpretation of the statutory terms "new drug," "grandfathered," and "GRASE" are unchanged and the HHS Notice did not affect the requirements that apply to new drugs under the statutes FDA administers. The HHS Notice did not, and legally could not, provide a new pathway for the legal marketing of unapproved new drugs. Neither HHS nor FDA has the authority to exempt a product or class of products that are new drugs under the FD&C Act from the new drug approval requirements of the FD&C Act. See *Cutler* v. *Kennedy,* 475 F. Supp. 838, 856 (D.D.C. 1979); *Hoffman-LaRoche* v. *Weinberger*, 425 F. Supp. 890, 892-894 (D.D.C. 1975).

Dated: May 17, 2021.

Janet Woodcock,
Acting Commissioner of Food and Drugs.

Dated: May 20, 2021.

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Xavier Becerra,

Secretary, Department of Health and Human Services.

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