Dated: December 15, 2021.

Lauren K. Roth,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2021–P–0375]

Determination That Alcohol and Dextrose Injection, 5 Milliliters/100 Milliliters, 5 Grams/100 Milliliters; and 10 Milliliters/100 Milliliters, 5 Grams/100 Milliliters, Were Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) has determined that Alcohol and Dextrose Injection, 5 milliliters (mL)/100 mL, 5 gram (g)/100 mL; and Alcohol and Dextrose Injection, 10 mL/100 mL, 5 g/100 mL, were withdrawn from sale for reasons of safety or effectiveness. The Agency will not accept or approve abbreviated new drug applications (ANDAs) for Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL; and 10 mL/100 mL, 5 g/100 mL.

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SUPPLEMENTARY INFORMATION: Section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)) allows the submission of an ANDA to market a generic version of a previously approved drug product. To obtain approval, the ANDA applicant must show, among other things, that the generic drug product: (1) Has the same active ingredient(s), dosage form, route of administration, strength, conditions of use, and, with certain exceptions, labeling as the listed drug, which is a version of the drug that was previously approved; and (2) is bioequivalent to the listed drug. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

Section 505(j)(7) of the FD&C Act requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the ''Approved Drug Products With Therapeutic Equivalence Evaluations,'' which is known generally as the ''Orange Book.'' Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made prior to approving an ANDA that refers to the listed drug (§ 314.161 (21 CFR 314.161)). FDA may not approve an ANDA that does not refer to a listed drug.

Between 1938 and 1968, FDA evaluated NDAs solely on the basis of safety information. In 1962, the Kefauver-Harris Drug Amendments (Pub. L. 87–781) amended the FD&C Act to require that new drug products also be shown to be effective in order to obtain approval of an NDA. After the enactment of the Kefauver-Harris Drug Amendments, FDA initiated the Drug Efficacy Study Implementation (DESI) to evaluate the effectiveness of drug products that had been approved between 1938 and 1962 solely on the basis of safety.

FDA introduced the concept of an ''abbreviated new drug application'' in 1968 as a vehicle for approval of certain drugs affected by the DESI review. When a drug product subject to the DESI review was determined to be effective for one or more indications, FDA would issue a **Federal Register** notice for that drug product describing the DESI review findings and stating whether abbreviated new drug applications that met specified criteria could be submitted to FDA (see generally 35 FR 11273 (July 14, 1970); 35 FR 6574 (April 24, 1970)) for products that had not been marketed under an NDA. Such a finding allowed manufacturers to submit an abbreviated new drug application in lieu of an NDA. For approval of these applications, which were submitted before the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) (Pub. L. 98–417) created the current ANDA pathway, FDA relied on the evidence of effectiveness that had been provided, reviewed, and accepted during the DESI process and evaluated the safety of these drug products on the basis of information included in NDAs submitted prior to 1962, as well as the subsequent marketing experience with the drugs. These applications are referred to as pre-Hatch-Waxman abbreviated new drug applications or ''PANDAs''.[1] PANDAs were submitted under section 505(b) of the FD&C Act and approved for safety and effectiveness under section 505(c) of the FD&C Act (see 86 FR 44731 at 44732 (August 13, 2021)).

As explained above, the current ANDA pathway is described in section 505(j) of the FD&C Act. Because of substantive differences in the application approval pathway for PANDAs, which were approved for safety and effectiveness under section 505(c) of the FD&C Act, compared to ANDAs approved under section 505(j) of the FD&C Act, FDA has determined that PANDA products can serve as reference listed drugs for 505(j) ANDA applicants seeking to make generic versions of these products and that there is a finding of safety and effectiveness that may be relied upon for approval by applicants of 505(b)(2) applications.

Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL; and 10 mL/100 mL, 5 g/100 mL, is the subject of NDA 004589, held by B. Braun Medical Inc. The initial application, which included Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL, was allowed to take effect on February 21, 1942. Alcohol and Dextrose Injection, 10 mL/100 mL, 5 g/100 mL, was allowed to take effect in a supplemental application on January 17, 1946. On July 28, 1972, FDA published a **Federal Register** notice regarding the DESI review of NDA 004589 (see 37 FR 15184). Under the DESI review, FDA concluded that there was substantial evidence of efficacy for two formulations of 5 percent Alcohol and 5 percent Dextrose for the indication ''for increasing caloric intake.'' Based on the **Federal Register** notice, FDA approved Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL in three PANDAs: ANDA 083263, held by Hospira, Inc. and initially approved on February 26, 1974; ANDA 083483, held by Miles Laboratories Inc. and originally approved on November 22, 1974; and

[1] See ''Drug Products Approved in Abbreviated New Drug Applications Before the Enactment of the Hatch-Waxman Amendments; Establishment of a Public Docket; Request for Comments,'' 86 FR 44731 (August 13, 2021). Note that the scope of the referenced notice is limited to drug products approved in PANDAs under section 505 of the FD&C Act prior to the Hatch-Waxman Amendments; the notice does not cover applications for antibiotic drug products that were originally submitted under section 507 of the FD&C Act (21 U.S.C. 357).

ANDA 083256, held by Baxter Healthcare Corp. and initially approved on March 12, 1976.[2]

All Alcohol and Dextrose Injection products have been discontinued and moved to the ''Discontinued Product List'' section of the Orange Book. In a letter dated June 23, 1999, Miles Laboratories Inc. notified FDA that Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL, the subject of ANDA 083483, was being discontinued, and FDA moved the drug product to the ''Discontinued Drug Product List'' section of the Orange Book. In the **Federal Register** of September 22, 1999, FDA announced it was withdrawing approval of ANDA 083256, effective September 22, 1999 (see 64 FR 51325). Approval of ANDA 083256 was withdrawn upon request of Baxter Healthcare Corp. under § 314.150(c) (21 CFR 314.150(c)) because the product was no longer being marketed. In the **Federal Register** of June 19, 2014, FDA announced it was withdrawing approval of ANDA 083263, effective July 21, 2014 (see 79 FR 35170). Approval of ANDA 083263 was withdrawn upon request of Hospira, Inc., under § 314.150(c) because the product was no longer being marketed. In the **Federal Register** of October 13, 2015, FDA announced it was withdrawing approval of NDA 004589, effective November 15, 2015 (see 80 FR 61426). Approval of NDA 004589 was withdrawn upon request of B. Braun Medical Inc. under § 314.150(c) because the products were no longer being marketed.

Celerity Pharmaceuticals, LLC submitted a citizen petition dated April 12, 2021 (Docket No. FDA–2021–P–0375), under 21 CFR 10.30, requesting that the Agency determine whether B. Braun Medical Inc.'s Alcohol and Dextrose Injection, 10 mL/100 mL, 5 g/100 mL, NDA 004589, was withdrawn from sale for reasons of safety or effectiveness. Although the citizen petition did not address the 5 mL/100 mL, 5 g/100 mL strength or the PANDAs, that strength and the PANDAs have also been withdrawn from sale. On our own initiative, we have also determined whether the 5 mL/100 mL, 5 g/100 mL strength under NDA 004589 and the PANDAs were withdrawn from sale for safety or effectiveness reasons.

The petitioner has identified no data or other information suggesting that Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL; or 10 mL/100 mL, 5 g/100 mL, were withdrawn for reasons of safety or effectiveness. Specifically, the petitioner states that the Alcohol and Dextrose Injection, 10 mL/100 mL, 5 g/100 mL, was discontinued for unknown reasons. The petitioner also included a letter published on November 15, 2005, in the *American Journal of Health-System Pharmacy,* which describes the use of Alcohol and Dextrose Injection as a treatment for ethylene glycol and methanol poisonings.

We have carefully reviewed our files for records concerning the withdrawal of Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL; and 10 mL/100 mL, 5 g/100 mL, from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. Based on a thorough evaluation of the information we have available to us and an evaluation of the latest version of the drug products' approved labeling, we have determined that the drug products would not be considered safe and effective if they were reintroduced to the market today. Therefore, after considering the citizen petition and reviewing Agency records and based on the information we have at this time, FDA has determined under § 314.161 that Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL; and Alcohol and Dextrose Injection, 10 mL/100 mL, 5 g/100 mL were withdrawn for reasons of safety or effectiveness.

Alcohol and Dextrose Injection is indicated to provide increased caloric intake. The use of Alcohol and Dextrose raises several safety concerns because there are many risks associated with the exposure to alcohol. Alcohol is contraindicated for use in patients with neurologic disorders, such as seizures, who have current or past substance abuse problems or who are pregnant. It can cause intoxication, respiratory depression, and disturbances in serum glucose levels. FDA-approved alternatives for intravenous calorie supplementation that do not include alcohol were approved after these Alcohol and Dextrose products and are available today.

In addition to the safety considerations, we have concerns about the appropriateness of Alcohol and Dextrose Injection to provide intravenous nutrition. Alcohol and Dextrose Injection was developed prior to the advent of more physiologically complete intravenous nutrition options. Parenteral nutrition, delivered intravenously, is used as a source of nutrition when oral or enteral nutrition cannot be administered. Parenteral nutrition is an admixture of solutions containing dextrose, amino acids, electrolytes, vitamins, minerals, and trace elements. Lipid emulsions are infused separately or added to the mixture, which allows for high energy supply with iso-osmolar solutions. Providing an adequate proportion of the energy needs as lipids obviates the need for high glucose infusion rates and, therefore, can contribute to the prevention of hepatic steatosis and hyperglycemia. Lipid emulsions are also necessary to supply essential fatty acids. Today, there are several FDA-approved parenteral products that are alternatives to Alcohol and Dextrose for increasing caloric intake and that also address other nutritional needs.

Because new clinical studies would first need to be conducted to address the concerns described above, FDA has determined that these Alcohol and Dextrose products would not be considered safe and effective if they were reintroduced to the market. Therefore, under § 314.161, FDA has determined that Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL; and 10 mL/100 mL, 5 g/100 mL were withdrawn for safety and effectiveness reasons. Accordingly, the Agency will remove B. Braun Medical Inc.'s NDA 004589 for Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL; and 10 mL/100 mL, 5 g/100 mL; Miles Laboratory Inc.'s ANDA 083483 for Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL; Baxter Healthcare Corp's ANDA 083256 for Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL; and Hospira, Inc.'s ANDA 083263 for Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that refer to these drug products.

Dated: December 15, 2021.

Lauren K. Roth,

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[2] The Orange Book refers to the Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL products in the three PANDAs (*i.e.,* ANDA 083263, ANDA 083483, and ANDA 083256) as Alcohol ''in'' Dextrose, but these products contain the same concentrations of alcohol and dextrose as Alcohol and Dextrose Injection, 5 mL/100 mL, 5 g/100 mL, approved under NDA 004589. Our findings are limited to these products, which contain both alcohol and dextrose, and we make no findings about the safety or effectiveness of any product that may contain only one of the active ingredients.