DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

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BY E-MAIL AND UPS

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Re: Diphoterine® Skin Wash, Request for Designation
On Remand to FDA, *Prevor v. FDA* (Civil Action No. 13-1177)

Dear Mr. Gibbs and Ms. Walsh:

This letter concerns Diphoterine Skin Wash, a product manufactured by your client, Prevor. On May 24, 2013, FDA issued a classification and jurisdictional assignment decision for Diphoterine Skin Wash. On September 9, 2014, the Honorable Rosemary M. Collyer of the United States District Court for the District of Columbia (District Court or Court) vacated FDA's determination and remanded the case to the agency for further action consistent with its opinion. *Prevor v. FDA*, No. 13-1177, 2014 WL 4459174, at *12 (D.D.C. Sept. 9, 2014) ("*Prevor II*"). FDA has carefully reconsidered the classification and jurisdictional assignment of Diphoterine Skin Wash in light of the Court's decision. As explained below, FDA determines that under the relevant statutory language and consistent with the Court's ruling, the diphoterine solution in Diphoterine Skin Wash is a drug and the canister that delivers the solution is a device. Therefore, Diphoterine Skin Wash is a drug-device combination product. FDA further determines that the drug constituent part—*i.e.,* the diphoterine solution—provides the primary mode of action of the product. Accordingly, the Center for Drug Evaluation and Research is the appropriate lead agency Center for premarket review and regulation of Diphoterine Skin Wash.

I. Procedural History

A. Prevor I

On August 13, 2009, Prevor submitted a Request for Designation to FDA's Office of Combination Products for its product, Diphoterine Skin Wash. Prevor requested that the Office of Combination products classify Diphoterine Skin Wash as a device and assign it to FDA's Center for Devices and Radiological Health for further evaluation. A.R. 1-2. The Office of Combination Products found that Diphoterine Skin Wash was a combination product (*i.e.,*

consisting of two constituent parts–a drug solution and a canister device) and that the drug constituent part (*i.e.,* the diphoterine solution) provided the primary mode of action of the product, making regulation by FDA's Center for Drug Evaluation and Research appropriate. A.R. 675-677. Prevor submitted a request for supervisory review under 21 C.F.R. § 10.75 to FDA's Office of Special Medical Programs, which affirmed the decision. A.R. 725; 784-789.

Thereafter, Prevor filed suit in the District Court, challenging FDA's determination. After cross motions for summary judgment, the Court issued its opinion on September 25, 2012, concluding that FDA acted arbitrarily and capriciously in its designation of Diphoterine Skin Wash when it: (1) relied on a statutory interpretation of the device exclusionary clause that treated *any* purpose of the product as a primary intended purpose; and (2) read the statute in such a way that "achievement *even in part* of *any* purpose" through chemical action was sufficient for exclusion, thus, preventing a device from having even a *de minimis* chemical action. *Prevor v. FDA*, 895 F. Supp. 2d 90, 92, 100-01 (D.D.C. 2012) ("*Prevor I*"). However, the Court provided FDA with the opportunity to explain its decision "without resort to its extra-statutory interpretations," and expressly reserved the possibility that the agency would conclude again that Prevor's diphoterine solution is not a device. *Id.* at 101. The Court also noted that it "does not question FDA's expertise," but found that the agency insufficiently explained its rationale for assigning Diphoterine Skin Wash to the Center for Drug Evaluation and Research while Reactive Skin Decontamination Lotion, an apparently similar product, is regulated by the Center for Devices and Radiological Health. *Id.* at 100. The Court vacated FDA's determination and remanded the case to the agency for further action consistent with its opinion. *Id.* at 101.

On May 24, 2013, FDA issued a detailed remand decision in response to the Court's order. A.R. 839. FDA again determined that Diphoterine Skin Wash is a drug-device combination product consisting of a drug solution and a device canister, and that the "primary mode of action" of the combination product is provided by the drug solution, making the Center for Drug Evaluation and Research the appropriate Center for regulation. *Id.* In finding that the diphoterine solution constituent part[1] of Diphoterine Skin Wash is excluded from the device definition because it "achieve[s] its primary intended purposes through chemical action," FDA first acknowledged that the agency had erred in its initial characterization of Diphoterine Skin Wash's primary intended purposes (*i.e.,* to wash chemical off the skin and neutralize the chemical on the skin) by conflating *how* the product may achieve its intended purpose (*i.e.,* washing and neutralizing) with *what* the product is intended to achieve (*i.e.,* help prevent and minimize accidental chemical burns). Accordingly, FDA re-evaluated the evidence and determined that Diphoterine Skin Wash had a single primary intended purpose, namely, to help prevent and minimize accidental chemical burn injuries. A.R. 843.

FDA then explained that it interpreted the statutory language, "achieve[s] its primary intended purposes through chemical action," to bar a product from being a device if chemical action "meaningfully contributes to" its primary intended purposes. Because the diphoterine solution's chemical action meaningfully contributed to its primary intended purpose of helping to prevent and minimize accidental chemical burns, FDA determined that the solution was excluded from

[1] The classification of the canister as a device constituent part of Diphoterine Skin Wash is not in question.

the device definition. A.R. 846. FDA proceeded to once again determine that the drug solution, and not the device canister, provided the primary mode of action of the product, so that assignment to CDER was appropriate.[2] A.R. 852. Finally, FDA more fully explained its rationale for assigning allegedly similar products differently. A.R. 857-859.

B. Prevor II

On August 1, 2013, Prevor brought a second challenge under the Administrative Procedure Act in the District Court. Cross-motions for summary judgment followed. The Court's September 9, 2014, decision granted in part and denied in part Prevor's motion for summary judgment and denied the government's motion for summary judgment ("*Prevor II*"). In *Prevor II*, the Court found in favor of FDA with respect to a number of significant issues, including:

- that Diphoterine Skin Wash has one "primary intended purpose": to "help prevent and minimize accidental chemical burns," *see* 2014 WL 4459174 at *7;

- that FDA had adequately explained its basis for treating allegedly similar products differently, *id.* at *11, n.9.[3]

However, the Court rejected FDA's interpretation that the statutory language "achieve[s] its primary intended purposes through chemical action" excludes a product from the device definition if the product's chemical action "meaningfully contributes to" its primary intended purposes. *Id.* at *6, *8-10. The Court found that because "meaningfully contributes to" is not synonymous with the statutory term "achieves," the law does not permit FDA to exclude a product from the device definition based on a "meaningfully contributes" standard. *Id.* at *6, *8-9. The Court explained that, to the contrary, under the statutory definition, the product's chemical action must "achieve"—*i.e.*, carry out successfully, accomplish, or attain—the product's primary intended purposes. *Id.* at *8-9. Importantly, the Court noted that it affords

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[2] In addition, FDA's remand decision explained that, even assuming *arguendo* that Prevor's interpretation of the relevant statutory language was correct (*i.e.*, that a product must achieve its primary intended purposes "predominantly" through chemical action to be excluded from the device definition), Prevor's data and information failed to demonstrate that the diphoterine solution achieves its primary intended purposes predominantly through physical, rather than chemical, action. A.R. 856.

[3] Specifically, the Court stated:

> Prevor also disputes that, on remand, FDA made logical distinctions between DSW and analogous products. However, FDA's analysis of the differences between products is not so unreasonable as to require rejection and a ruling that DSW must be classified as a device. *See Am. Forest Res. Council v. Ashe*, 946 F. Supp. 2d 1, 19 (D.D.C. 2013) (finding that while record might support more than one conclusion, the conclusion drawn by agency after changing its approach did not have to be only, or even best, conclusion—only had to be rational because decision was scientific determination to which Court owed particular deference).

Given that Prevor's arguments concerning FDA's basis for distinguishing allegedly similar products were rejected by the Court in *Prevor II* and the Court, instead, found that FDA had adequately explained its basis for treating allegedly similar products differently, it is unnecessary for FDA to revisit arguments related to these products in this remand decision.

deference to the agency's scientific analysis, expressly acknowledging that "[o]n remand, FDA could find that [Diphoterine Skin Wash] should be classified as a drug-device combination product with a drug mode of action if it also adopts a plausible construction of the relevant statutory language." *Id.* at *10.

II. Analysis

Diphoterine Skin Wash consists of two constituent parts: diphoterine solution and a pressurized canister that delivers the diphoterine solution onto the skin. As the Court acknowledged, FDA and Prevor agree that the pressurized canister is a device under the FD&C Act. *Id.* at *8. The issue for FDA to determine on remand is whether the diphoterine solution in Diphoterine Skin Wash is properly considered a device or a drug under the FD&C Act. If the diphoterine solution is a device, then Diphoterine Skin Wash as a whole would be considered a device only and assigned to the Center for Devices and Radiological Health, because the canister is also a device. *See* 21 C.F.R. 3.2(e) (definition of "combination product" excludes device/device combinations). In contrast, if the solution is a drug, then Diphoterine Skin Wash as a whole would be considered a drug-device combination product. As a combination product, Diphoterine Skin Wash would be assigned to a lead Center based on its "primary mode of action" under section 503(g) of the FD&C Act and FDA's implementing regulations in 21 C.F.R. 3.4.

Section II.A of this remand decision sets forth FDA's determination that Prevor's diphoterine solution is a drug and not a device under the FD&C Act. Section II.B sets forth FDA's determination that, under FDA's combination product statute and regulations, the appropriate lead Center for premarket review and regulation of Diphoterine Skin Wash is the Center for Drug Evaluation and Research.

A. Prevor's Diphoterine Solution is a Drug and Not a Device under the FD&C Act

Under the FD&C Act's definition of device, a product is excluded from being a device if it "achieve[s] its primary intended purposes through chemical action within or on the body of man."[4] The drug definition contains no such exclusion.[5] Based on its review of Prevor's

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[4] Under section 201(h) of the FD&C Act, a device is defined, in part, as:

> an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of diseases, in man or other animals, or . . . intended to affect the structure or any function of the body of man or other animals, and which *does not achieve its primary intended purposes through chemical action* within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

21 U.S.C. § 321(h) (emphasis added).

[5] Under section 201(g) of the FD&C Act, a drug is defined, in part, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and . . . articles (other than food) intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. § 321(g)(1)(B) & (C).

characterization of its product, FDA concludes that Prevor's diphoterine solution has one "primary intended purpose": to help prevent and minimize accidental chemical burns. The Court upheld this conclusion in *Prevor II*. *See* 2014 WL 4459174 at *7.[6] Whether Prevor's diphoterine solution is a device or a drug therefore hinges on whether it "achieves"—meaning "carries out successfully"; "accomplishes"; or "attains"—this primary intended purpose of "help[ing] to prevent and minimize accidental chemical burns" through chemical action. *Id.* at *8-9.

The first question in determining whether Prevor's diphoterine solution "achieves" its primary intended purpose through chemical action is whether the solution has chemical action. The solution consists of diphoterine in water. As noted by Prevor, the water in the solution enables the diphoterine to be chemically active, rendering it capable of neutralizing acids and bases. A.R. 4. As Prevor explained in its Request for Designation:

> The neutralization effect of [diphoterine solution] is attributable to the fact that [diphoterine solution] is a polyvalent and an amphoteric solution. Its polyvalent characteristics allow [diphoterine solution] to interact with more than one type of chemical. [Diphoterine solution] is amphoteric, Lewis type, capable of neutralizing an acid or a base. It forms covalent bonds with both acids and bases. Once the bond is formed, the acid or base becomes a neutral salt. [Diphoterine solution] attracts acidic substances to its basic site and vice versa. A bond is formed between [diphoterine solution] and the acid or base, and the offending chemical becomes inactive because it bonded with [diphoterine solution].

A.R.3-4. Similarly, in its 10.75 Request, Prevor stated that, in the presence of acids or bases, the diphoterine solution bonds to the acid or base, and that once the bond is formed, "the acid or base becomes a neutral salt." A.R. 729.

Prevor's characterization of the chemical neutralization action of diphoterine in solution is consistent with a paper authored by affiliates of Prevor and published in a peer-reviewed journal in 2007. Specifically, the paper describes diphoterine as a "water-soluble, amphoteric molecule . . . with multiple binding sites capable of reacting with corrosives and irritants and preventing or decreasing their action on the tissues." A.R. 448.[7] Therefore, based on the information in Prevor's submissions to FDA and published

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[6] As noted by the Court, this was the purpose advanced by Prevor itself in its Request for Designation. 2014 WL 4459174 at *7 (citing A.R. 2). Moreover, as the Court also acknowledged, this characterization is consistent with the language of the device definition. The primary intended purpose of a product must be something other than a method of action; otherwise, the device definition would not specify that the primary intended purpose could be achieved by a method of action. *Id.*

[7] Mathieu L, F Burgher, J Blomet, Comparative evaluation of the active eye and skin chemical splash decontamination solutions Diphoterine and Hexafluorine with water and other rinsing solutions: effects on burn severity and healing, J Chem Health Safety, 2007 14(4): 32-39.

scientific literature, FDA concludes that Prevor's diphoterine solution has at least one type of "chemical action" under the device definition: chemical neutralization.[8]

Having determined that Prevor's diphoterine solution has chemical action, the next question is whether it achieves its primary intended purpose—*i.e.*, to help prevent and minimize accidental chemical burns—through such chemical action. As noted in FDA's May 24, 2013 remand decision, Prevor has not yet established that Diphoterine Skin Wash can, in fact, achieve its primary intended purpose of "help[ing] prevent and minimize accidental chemical burns." FDA will not undertake a review of Diphoterine Skin Wash's effectiveness (or safety) until Prevor submits an application for the product's marketing authorization.[9] Therefore, to apply the device definition's chemical action exclusion to Prevor's product, FDA must answer a hypothetical question: assuming Prevor's diphoterine solution is capable of "help[ing] prevent and minimize accidental chemical burns," would it achieve this purpose through chemical action?[10] As described below, based on its careful consideration of the relevant data and information, FDA concludes that the answer is yes. Assuming that Prevor's diphoterine solution is capable of "help[ing] prevent and minimize accidental chemical burns," it would be expected to achieve this purpose through its chemical neutralization.

1. Etiology of Chemical Burns

As an initial matter, general scientific understanding of the etiology of chemical burns suggests that the diphoterine solution would achieve prevention and minimization of chemical burns through its chemical action. A chemical burn occurs when living tissue is exposed to a corrosive chemical agent such as a strong acid or base. Chemical burns may occur immediately on contact and can cause extensive tissue damage, including damage to structures under the skin. The damage to living tissue is mainly due to acid-base reactions that destroy proteins and lipids. The chemical reaction that destroys proteins is due to the hydrolysis and destruction of the amide bonds which hold these molecules together. Similarly, the ester bonds that hold many

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[8] FDA's decision on remand from *Prevor I* also addressed Prevor's statements on its website concerning the diphoterine solution's hypertonic action. Recent letters from Prevor's counsel assert that hypertonic action should not be considered "chemical action" under the device definition. Although we do not agree with Prevor on this issue, we have determined that we need not address those arguments here because, as explained in this remand decision, we conclude that Prevor's diphoterine solution achieves—*i.e.*, accomplishes or attains—its primary intended purpose of "help[ing] prevent and minimize accidental chemical burns" through its chemical neutralization action. As noted, Prevor acknowledged in its Request for Designation and 10.75 Request that the diphoterine solution's chemical neutralization action is a type of chemical action.

[9] Prevor earlier submitted but then withdrew a premarket notification (510(k)) submission after the Center for Devices and Radiological Health notified the company that Diphoterine Skin Wash may be a combination product with a drug primary mode of action.

[10] For ease of reading, we often use "achieve" instead of "would be expected to achieve" in this decision letter, but this should not be read to imply that FDA has concluded that Prevor's Diphoterine Skin Wash product is effective.

lipids together are also decomposed by bases or acids.[11] Therefore, assuming that Prevor is correct that its diphoterine solution can bind to acids and bases on contact[12] and neutralize them, this chemical action would achieve prevention and minimization of chemical burns by stopping the problem at the source, quickly converting the corrosive agent into a harmless one.[13]

2. Industry Standards for Portable Emergency Showers

Comparing Diphoterine Skin Wash to an emergency shower—as Prevor itself has done in its submissions to FDA—is also revealing. In its Request for Designation, Prevor describes Diphoterine Skin Wash as "a substitute for water showers at the workplace." A.R. 4. According to published standards, however, a portable emergency shower for the prevention and minimization of chemical burns in an industrial workplace must be capable of delivering a minimum of *20 gallons of water per minute for 15 minutes*. A.R. 855. It is clear that Prevor's product would be incapable of delivering anything close to this volume of fluid. According to Prevor's Request for Designation, the product would be sold in canisters that hold 3.4 ounce (100 ml, less than ½ cup of fluid), 6.8 ounce (200 ml, just over ¾ cup of fluid), and 5 liters (just over one gallon) of the diphoterine solution. A.R. 2-3, 57. Additionally, although Prevor provided no data on the force with which its diphoterine solution is delivered by the canister, it describes the canister as delivering the liquid as an "aerosolized mist"—suggesting that its force is far weaker than that provided by a portable emergency shower delivering 20 gallons of water per minute. A.R. 164. These stark differences in flushing volume and force provide additional support for the conclusion that, if Prevor's Diphoterine Skin Wash is in fact capable of preventing and minimizing accidental chemical burns, this would be due to its chemical action.

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[11] Nehles J, Hall A, Blomet J, and Mathieu L, Diphoterine For Emergent Decontamination of Skin/Eye Chemical Spashes: 24 Cases, Cutaneous and Ocular Toxicology, 2006 25: 249-258 (explaining that "[c]hemical agents do not 'burn' in the classic sense of tissue destruction by heat. Rather they act by coagulating proteins through oxidation, reduction, salt formation, corrosion, protoplasmic poisoning, metabolic competition or inhibition, dessication, or vesicant activity and resultant ischemia.") A.R. 87.

[12] During the *Prevor II* litigation, Prevor claimed for the first time that the neutralization effect of the diphoterine solution occurs "after" the physical action of the product "already has achieved" prevention and minimization of chemical burns. *Prevor II* Pl.'s Opp'n at 27. There is no evidence in the record to support this assertion, as none of the studies Prevor submitted provided a basis to evaluate the time course of the diphoterine solution's neutralization action. Moreover, the video Prevor submitted with its Request for Designation suggests that the diphoterine solution would neutralize harmful chemicals upon contact. Specifically, it shows fluid spilled on the user's hand (representing a chemical spill) that quickly loses its color and becomes transparent when the diphoterine solution is sprayed on the hand, apparently because of the solution's neutralization effect (assuming the color change indicates a change in pH).

[13] This also assumes, *arguendo*, that the diphoterine active ingredient is safe for this use.

3. Published Literature on the Effects of Diphoterine in Solution

FDA conducted an extensive review of available published literature concerning the use of diphoterine in solution to prevent and minimize chemical burn injuries.[14] This published literature included papers that discussed clinical observations, case studies, *in vivo* studies, and *in vitro* studies. Each of the studies emphasized the diphoterine solution's ability to prevent or minimize chemical burn injuries through its chemical action. The studies included the following:

- Two very similar animal studies published in 2004 that evaluated the effect of diphoterine solution on chemical burn injuries in rats.[15] As described in the publications, twenty rats were randomly assigned to one of four groups (five rats per group). A chemical burn injury was created by applying 0.5 ml of 52% hydrochloric acid for 15 seconds to the back of each animal. The burns on five animals were not rinsed; the burns on the other three groups were rinsed with one of three solutions: saline, calcium gluconate, or diphoterine solution. Wound healing after seven days was found to be most successful in the diphoterine-treated group.[16] Because all of the solutions studied were delivered in the same manner (rinsing for 30 seconds at approximately 50 ml/min) and likely shared similar physical displacement effects, it is reasonable to attribute the diphoterine solution's relative success in promoting wound healing to its chemical action. Indeed, a peer-reviewed 2007 retrospective review posited that the reason the diphoterine rinse was more effective than the saline rinse in these two animal studies was because "[d]iphoterine stopped the development of the chemical burn." A.R. 451.

- A 2005 paper, authored by affiliates of Prevor, that describes case studies in which five volunteer study subjects used 250 mL of diphoterine solution dispensed from a "low pressure spray container" to prevent and minimize adverse eye and skin effects caused by exposure to ortho-chlorobenzylidene malononitrile tear gas.[17] The paper describes diphoterine as:

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[14] Prevor has argued that it was improper for FDA to consider these published studies. *Prevor II* Pl.'s Mem. at 10. However, as noted by the Court, FDA "may review published literature about the product or product ingredients if relevant to product classification or assignment, for example, published results from *in vitro* studies, animal testing, clinical testing, and/or case histories." 2014 WL 4459174 at *10, n.8.

[15] Cavallini M and A Casati, A prospective, randomized, blind comparison between saline, calcium gluconate and diphoterine for washing skin acid injuries in rats: effects on substance and β-endorphin release, Eur J Anaesthesiol, 2004 21(5): 389-392, A.R. 860-863; Cavallini M, F de Boccard, MM Corsi et al., Serum pro-inflammatory cytokines and chemical acid burns in rats, Annals Burns Fire Disasters, 2004 17(2): 84-87), A.R. 864-867.

[16] Although this study endpoint possibly differs slightly from Diphoterine Skin Wash's primary intended purpose (to help prevent and minimize accidental chemical burns), we nonetheless consider these data to be relevant because one aspect of minimizing chemical burn injury is to improve wound healing post-burn injury; successful treatment will lessen the severity of the wound (injury).

[17] Viala B, Blomet J, Mathieu L, and Hall A, Prevention of CS "Tear Gas" Eye and Skin Effects and Active Decontamination with Diphoterine: Preliminary Studies in 5 French Gendarmes, J. of Emergency Medicine, 2007, 29(1): 5-8. A.R. 71-74.

> an active eye and skin decontamination solution that has been tested and safely used for eye and skin splashes with a wide variety of irritant and corrosive chemical compounds, including acids, bases, oxidizing agents, reducing agents, alkylating agents, and solvents. It is a polyvalent, amphoteric, hypertonic, chelating compound with six active binding sites for the above types of chemicals.

A.R. 71. According to the authors, when study subjects who had been exposed to tear gas immediately applied the diphoterine solution using the low-pressure spray container, "[a]ll signs and symptoms [resulting from exposure to the tear gas] resolved in less than 3 min. No ocular burns, facial burns, or photophobia were noted." A.R. 73.

- A 2006 paper, authored by affiliates of Prevor, describing case reports of diphoterine skin/eye chemical splash emergent decontamination in a group of 24 German metallurgy workers.[18] The authors state that "[d]iphoterine decontamination . . . has been found to prevent or decrease the severity of burns, to rapidly decrease pain, and has resulted in fewer requirements for medical or surgical burn care[.]" A.R. 93. The authors explain that their review of the 24 case reports revealed that diphoterine decontamination "prevented burns" even in those workers who had eye or skin exposure to concentrated corrosives. *Id.* The authors note that similar exposures to strong and concentrated corrosives have been reported to cause severe burns when water (as opposed to diphoterine) decontamination was done immediately. *Id.* at 93-94.

- A 2007 paper, authored by affiliates of Prevor, in which the authors review clinical observations, case studies, *in vivo* studies, and *in vitro* studies concerning the use of diphoterine solution to prevent and minimize chemical burn injuries. The authors characterize diphoterine as a "water-soluble, amphoteric molecule . . . with multiple binding sites capable of reacting with corrosives and irritants and preventing or decreasing their action on the tissues." A.R. 448. The authors describe an *in vitro* study similar (in design, not in conclusions) to Prevor's Study II, described below in Section II.A.4, in which diphoterine solution or water is added to a beaker containing an acid or base. Much less volume of the diphoterine solution was apparently needed, as compared to water, to bring the pH of the acid or base to within a range characterized as non-harmful. The authors conclude that diphoterine was superior to water at changing the pH of the acid or base because "[d]iphoterine, as an amphoteric compound, has bound both the base and the acid and reacted with it, returning the pH to a [non-harmful] physiological state (between 5.5 and 9)." A.R. 449.

- A 2007 paper that describes a skin sensitization study funded by Prevor. The authors explain that diphoterine is "an amphoteric, slightly hypertonic, chelating compound which can actively bind to and inactivate a wide variety of chemical compounds splashed

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[18] Nehles J, Hall A, Blomet J, and Mathieu L, Diphoterine For Emergent Decontamination of Skin/Eye Chemical Spashes: 24 Cases, Cutaneous and Ocular Toxicology, 2006 25: 249-258. A.R. 87-96.

into the eyes or on the skin."[19] A.R. 79-80. The authors further state that "[t]he emergent use of Diphoterine prevents or decreases the severity of eye/skin burns and decreases the need for medical or surgical burn treatment, sequelae, and lost worktime." A.R. at 75. The authors also note that "[t]he rapid amelioration of pain during Diphoterine decontamination of chemical splashes" was observed in a human occupational chemical exposure study. A.R. at 80.

- Two 2010 papers,[20] one of which was authored by affiliates of Prevor and described bench studies that showed that diphoterine solution is "more beneficial than tap water" in preventing and minimizing chemical burns "as the pH decreased more rapidly to a value where burns are usually not observed."[21] A.R. 879. The other 2010 study compared Diphoterine Skin Wash to an industrial shower for preventing and mitigating burns and concluded that "'[a]pplying Diphoterine first was associated with significantly better outcomes following alkalai skin splashes than applying water first."[22] A.R. 873.

4. Prevor's Characterization of Diphoterine Skin Wash on its Public Website

FDA also reviewed Prevor's characterization of Diphoterine Skin Wash on its public website. Prevor's website information clearly attributes the diphoterine solution's ability to achieve chemical burn prevention and minimization to its chemical action. For example, the website includes the following claims:

- Diphoterine Skin Wash "'[i]mprov[es] on rinsing with water" because of "[t]he improvements brought by [d]iphoterine to chemical decontamination." A.R. 51 (quoting Prevor's website).

- Diphoterine Skin Wash "stops the irritating and corrosive agents[']actions on the . . . skin, thanks to its amphoteric and chelating properties." *Id.*

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[19] Mathieu L, Burgher F, and Hall A, Diphoterine Chemical Splash Decontamination Solution: Skin Sensitization Study in the Guinea Pig, Cutaneous and Ocular Technology, 2007, 26: 181-187. A.R. 75-81.

[20] Neither of these articles is in the administrative record for FDA's initial classification decision for Diphoterine Skin Wash because they post-date that decision. FDA was entitled to consider information not in the original administrative record because the *Prevor I* Court asked FDA to reevaluate the scientific evidence. In any event, even without these 2010 articles, there is more than enough evidence to show that Prevor's diphoterine solution achieves its primary intended purpose of "help[ing] to prevent and minimize accidental chemical burns" through chemical action.

[21] Fosse C, Mathieu L, Hall A et al., Decontamination of tetramethylammonium hydroxide (TMAH) splashes: promising results with Diphoterine in vitro, Cutaneous Ocular Toxicology, 2010 29(2):110-115.

[22] Donoghue AM, Diphoterine for alkalai chemical splashes to the skin at alumina refineries, Int J. Dermatology, 2010 49(8):894-900.

- Diphoterine Skin Wash "has a prolonged intervention time compared to water (in the minute following the chemical splash) with improved rinsing effectiveness: absence of after-effects, no or little need for secondary care, and no or little loss of work." *Id.*

5. Studies and Information in Prevor's RFD

In its Request for Designation materials, Prevor described the results of two unpublished studies and provided a short video to support its claim that the physical washing effect of the diphoterine solution "provides the primary effect that contributes to the intended use, and the chemical effect of [the diphoterine solution] is secondary." A.R. 7. Specifically, Prevor claimed that the physical washing effect contributes "approximately 90%" of Diphoterine Skin Wash's overall effect and that chemical neutralization contributes "approximately 10%" of its effect. A.R. 1.

Not only is this "90 % physical/10 % chemical" claim wholly unsupported by the evidence Prevor submitted, Prevor's argument mistakes the relevant inquiry. In *Prevor II*, the Court did not articulate "predominance of physical action" as the standard for when a product falls within the scope of the device definition. Rather, the Court explained that, under the plain language of the statute, a product that "achieve[s]"—*i.e.*, accomplishes or attains— its primary intended purposes through chemical action is excluded from the device definition, whether or not it also has physical actions. *See* 2014 WL 4459174 at *9 ("The Act unambiguously specifies that the 'chemical action' must 'achieve' the product's primary purposes."). In any event, as described below, to the extent Prevor's data and information provide <u>any</u> basis to evaluate how the diphoterine solution would achieve prevention and minimization of chemical burns, they suggest that the diphoterine solution would achieve—*i.e.*, accomplish or attain—this purpose through chemical neutralization.

(i) Study I

In Study I, Prevor purports to have compared the physical displacement effect of diphoterine solution with the physical displacement effect of water. A.R. 5. In this study, a 10 ml glass beaker was placed inside an empty 250 ml glass beaker. A pH electrode was inserted inside the 10 ml beaker. Sodium hydroxide with a pH of 14—a strong base—was poured into the 10 ml beaker, filling it to the top. The diphoterine solution was then pipetted in 1 ml increments into the 10 ml beaker of sodium hydroxide. As the diphoterine solution was added to the beaker of sodium hydroxide, the contents of the full 10 ml beaker were allowed to overflow into the empty, larger beaker. The pH of the contents of the 10 ml beaker was measured to determine at what point it dropped to 9, a pH within the neutral range. The same process was then conducted with water, a substance that does not have the ability to neutralize a strong base. Prevor considered the pH of the solution in the beaker to be "an indicator of volume displacement . . . indicat[ing] that the [sodium hydroxide] had been physically displaced by the test solution" because water and diphoterine solution have a neutral pH. *Id.* The results showed that a pH of 9 was reached after pipetting 68 ml of diphoterine solution as compared to 149 ml of water. *Id.*

According to Prevor, Study I demonstrates that the diphoterine solution "has similar physical effects to those of water on the displacement of fluid" and that it has a "secondary chemical neutralization mechanism of action." *Id.* The study results do not support this conclusion,

however. On the contrary, the study found that *less than half as much* diphoterine solution as water was needed to reduce the measured pH in the sodium hydroxide solution from 14 (a strong base) to 9 (a neutral solution). *Id.*[23]

(ii) Study II

In Study II, Prevor purports to "confirm that volume displacement (or physical displacement) of the [sodium hydroxide], rather than chemical activity, was the main contributor to lowering the pH of the small beaker solution" in Study I. A.R. 6. In the study, diphoterine solution and water were each added to separate 250 ml beakers initially containing 10 ml of concentrated sodium hydroxide. When the solution in the beaker approached 250 ml, the contents were poured into a larger beaker and the serial addition of 1 ml volumes of diphoterine solution or water continued. The pH of the solution in each beaker was measured as the volume increased. The study found that 2250 ml of diphoterine solution were needed to reduce the pH of the sodium hydroxide in the beaker from 14 to 9. In contrast, according to Prevor's calculations, it would have taken 1000 liters of water to reduce the pH of the same amount of sodium hydroxide from 14 to 9. A.R. 6 (stating "it was calculated that approximately 1000 Liters of water alone would be needed to be diluted into the [sodium hydroxide] in order to decrease the pH of [sodium hydroxide] from 14 to 9.0"). *Id.*

According to Prevor, these study results demonstrate that "neutralization and dissolution play a very minor role in obtaining the overall effect of [diphoterine solution]" because, as compared with the method in Study I, it took 33 times more diphoterine solution to bring the pH of the sodium hydroxide from 14 to 9. A.R. 6. Prevor's conclusion is patently at odds with its own calculations. Based on Prevor's own calculations, in Study II, the diphoterine solution was far more effective than water at lowering the pH of the 10 ml of concentrated sodium hydroxide. Specifically, to achieve the same reduction in pH with water as with the diphoterine solution would require using a volume of water over *400 times* greater (1000 liters) than the volume of diphoterine solution (2250 ml) used to bring the pH of the concentrated sodium hydroxide from 14 to 9. *Id.* Indeed, as noted above in Section II.A.3, Prevor affiliates relied on a study conceptually similar to Study II to highlight the significance of the diphoterine solution's chemical action, not its relative unimportance. Additionally, as with Study I, because Study II involved studying the effects of the diphoterine solution on chemicals in a beaker, it does not provide a basis to evaluate the physical displacement effect of the solution under its actual conditions of use.

[23] Pipetting additional liquid directly into a beaker does not approximate spraying solution in aerosolized form onto the body. The study does not provide any basis to evaluate the volume of contaminants physically displaced from a person's skin by a given volume of aerosolized diphoterine solution delivered from a spray canister, which would likely depend on many factors, including the viscosity of the chemical spill, the degree to which the chemical penetrates the skin, how close the spray canister is to the skin when sprayed, the angle between the spray and the skin, the orientation of the contaminated area with respect to vertical.

(iii) Prevor's Video

Prevor also submitted a short video along with its Request for Designation that purportedly illustrates the diphoterine solution's effects. A.R. 718. The video shows fluid spilled on the user's hand (representing a chemical spill) that rapidly loses its color and becomes transparent when the diphoterine solution is sprayed on the hand, apparently because of the solution's neutralization effect (assuming the color change indicates a change in pH). It also shows the chemical spill dripping off the skin after the diphoterine solution is sprayed on. *Id.* The video provides no basis to evaluate the physical displacement effect of the solution.[24] It does, however, indicate that the diphoterine solution immediately begins to neutralize the chemical spill while the spill is still on the skin.

In sum, based on our review and analysis of the available data and information, we find that Prevor's diphoterine solution would achieve its primary intended purpose—*i.e.*, to help prevent and minimize accidental chemical burns—through its chemical neutralization action.[25] Accordingly, we determine that Prevor's diphoterine solution falls outside the scope of the FD&C Act's device definition. We further conclude that Prevor's diphoterine solution meets the FD&C Act's definition of "drug" because the diphoterine solution is an article intended to mitigate or prevent chemical burn injuries.[26]

B. Prevor's Diphoterine Skin Wash Should be Assigned to the Center for Drug Evaluation and Research Based on its Primary Mode of Action

Because we have determined that the diphoterine solution in Diphoterine Skin Wash is a drug and the pressurized canister is a device, we further conclude that Diphoterine Skin Wash as a whole is a combination product. *See* 21 C.F.R. 3.2(e)(1) (defining a "combination product" as, in relevant part, "[a] product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity").

Under the FD&C Act (21 U.S.C. 353(g)) and FDA's implementing regulations in 21 CFR Part 3, FDA must assign a combination product to a lead Center for premarket review and regulation based on the product's "primary mode of action." Under FDA's regulations, the relevant inquiry

[24] The skin absorption and biocompatibility studies that Prevor describes in its Request for Designation do not provide any support for Prevor's arguments that diphoterine solution should be classified as a device. Whether or not the solution is absorbed by the skin or is biocompatible does not alter its abilities to bond to and thereby neutralize acidic and basic chemicals spilled on the skin.

[25] Again, this assumes, *arguendo*, that Prevor's diphoterine solution is in fact capable of achieving this purpose.

[26] As noted, the FD&C Act defines "drug," in part, to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and . . . articles (other than food) intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. 321(g)(1)(B) & (C).

for determining "primary mode of action" is which constituent part provides the most important contribution to the combination product. 21 CFR 3.2(k) & (m); 21 CFR 3.4. This is because the "modes of action" of a combination product are determined by the definitional status (i.e., device, drug, biological product) of its constituent parts.[27] Each constituent part has one and only one "mode of action," and these "modes of action" are mutually exclusive (*e.g.*, a *drug* constituent part has a *drug* mode of action while a *device* constituent part has a *device* mode of action). 21 CFR 3.2(k). A constituent part that achieves its primary intended purposes through chemical action within or on the body can never have a "device mode of action," even if it also has a physical effect, because FDA's regulations provide that a constituent part cannot have a "device mode of action" unless it meets the device definition.[28]

Accordingly, under FDA's regulations, the diphoterine solution constituent part of Diphoterine Skin Wash has a "drug mode of action" but not a "device mode of action" because the solution meets the drug definition but not the device definition.[29] The canister constituent part has a "device mode of action" because it meets the device definition.

After identifying the "modes of action" of a combination product, the next step is to determine which is the "primary mode of action." Under 21 CFR 3.2(m), the "primary mode of action" of a combination product is defined as "the single mode of action . . . that provides the most

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[27] *See* 70 Fed. Reg. 49851 ("FDA . . . clarifies that the definition of [mode of action] relates only to the definitional status of each individual component [of a combination product].").

[28] Recognizing that the statutory definitions of "device," "biological product," and "drug" are overlapping, FDA's regulations ensure that each constituent part contributes only one "mode of action." 21 CFR 3.2(k) states that "*each constituent part* contributes a biological product, device, *or* drug mode of action..." (emphasis added). It further defines the three different modes of action such that a constituent part can provide only one mode of action. For example, a constituent part *cannot* have a "device mode of action" *unless* it meets the definition of device contained in 21 U.S.C. 321(h), does not have a "biological product mode of action," and does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and is not dependent upon being metabolized for the achievement of its primary intended purposes. 21 CFR 3.2(k)(2) (emphasis added). A constituent part that meets the device definition cannot have a "drug mode of action" because the definition of "drug mode of action" excludes, among other things, a constituent part that has a "device mode of action" as defined in 21 CFR 3.2(k)(2). 21 CFR 3.2(k)(3). *See also* 70 Fed. Reg. 49851 (recognizing that "mutually exclusive" mode of action definitions were necessary, in part, because "a device will also meet the statutory definition of drug").

[29] In its Request for Designation, Prevor argued that if Diphoterine Skin Wash were considered a drug-device combination product instead of a device, then it would have a device "primary mode of action" because—according to Prevor—the physical effect of the Diphoterine Skin Wash is "predominantly responsible" for achieving the overall intended use of the product. AR 5. This argument is inconsistent with FDA's regulations. The relevant inquiry for determining "primary mode of action" under 21 CFR Part 3 is which constituent part provides the most important contribution to the combination product, not whether the combination product as a whole works "predominantly" through chemical or non-chemical action. 21 CFR 3.2(k); 21 CFR 3.4. Moreover, the Court acknowledged that Prevor abandoned this alternative argument on summary judgment in the *Prevor II* litigation by arguing only that Diphoterine Skin Wash is a single-entity product. 2014 WL 4459174 at *2, n.2.

important therapeutic action of the combination product," *i.e.,* "the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product." Because the "modes of action" of a combination product are determined by its constituent parts, the "primary mode of action" of a combination product depends on *which constituent part is expected to make the greatest contribution to the product's overall intended therapeutic effects*. For example, a drug-device combination product has a drug "primary mode of action" if the drug constituent part is expected to make a greater contribution than the device constituent part to the product's overall intended therapeutic effects.

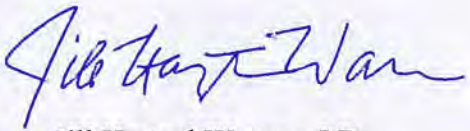
When we compare the relative contributions of Diphoterine Skin Wash's two constituent parts, it is clear that the drug constituent part—the diphoterine solution—is expected to make the greatest contribution to the overall therapeutic effects of the product. The drug is responsible for the therapeutic effect, helping to prevent and minimize chemical burn injuries; the device canister facilitates delivery of the drug by spraying it onto the skin in an aerosolized mist. Indeed, the drug solution could be delivered without the canister and still help prevent and minimize chemical burns, as reflected in the animal studies discussed in Section II.A.3 (where diphoterine solution was applied as a rinse, not as an aerosol spray).

We therefore conclude that Diphoterine Skin Wash has a drug "primary mode of action" and that it should be assigned to the Center for Drug Evaluation and Research as the Agency component with primary jurisdiction for premarket review and regulation. 21 U.S.C. 353(g)(1)(A); 21 CFR 3.4(a)(1). This assignment is consistent with other assignments of combination products in which we considered the device constituent part of a drug-delivery combination product (e.g., a canister or syringe pre-filled with a drug) to provide a less important contribution than the drug, resulting in a drug "primary mode of action." *See* 70 Fed. Reg. at 49854 (describing the assignment of pre-filled delivery systems to the Center for Drug Evaluation and Research).

III. Conclusion

For the reasons described above, we determine that the diphoterine solution in Diphoterine Skin Wash is a drug constituent part and that Diphoterine Skin Wash as a whole is a drug-device combination product. We further find that Diphoterine Skin Wash has a "drug" primary mode of action because the drug constituent part—*i.e.*, the diphoterine solution—is expected to make the greatest contribution to the overall therapeutic effects of the combination product. Accordingly, we are assigning Diphoterine Skin Wash to the Center for Drug Evaluation and Research as the Agency component with primary jurisdiction for premarket regulation.

Sincerely,



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