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CITIZEN PETITION

This Citizen Petition is submitted under 21 C.F.R. §§ 10.25(a) and 10.30 to request that the U.S. Food and Drug Administration ("FDA" or "Agency"):

1. Determine, based on current drug approval standards, that the Sodium Thiosulfate Injection drug product approved under New Drug Application ("NDA") #020166 was withdrawn from sale for reasons of safety or effectiveness; and
2. Refrain from receiving or approving any Abbreviated New Drug Application ("ANDA") submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") that identifies the Sodium Thiosulfate Injection drug product approved under NDA #020166 as the reference listed drug ("RLD").

The U.S. Army sponsored NDA #020166 for Sodium Thiosulfate Injection, and FDA approved the application in 1992 under exigent circumstances; namely, the drug was urgently needed as an antidote for acute cyanide poisoning for U.S. troops deployed to the Middle East as a part of Operation Desert Storm. The Sodium Thiosulfate Injection drug product approved under NDA

#020166 was discontinued by the U.S. Army in March 2004. Importantly, NDA #020166 no longer meets current approval standards. As explained below:

- Although NDA #020166 complied with the quality specifications listed in the U.S. Pharmacopeia (USP) monographs for sodium thiosulfate drug substance and drug product that were in effect in 1992, the 1992 monographs are no longer current and do not include the same tests as required in the corresponding current USP monographs. More fundamentally, FDA itself recently acknowledged that even the current USP monographs for sodium thiosulfate are "not sufficient . . . to ensure adequate product quality."[1] Under Section 501(a)(2)(B) of the FD&C Act, a drug product is adulterated if it does not conform with current "quality and purity characteristics."
- When the FDA-approved labeling for NDA #020166, which is now 30-years old, is compared to the labeling for more recently approved Sodium Thiosulfate Injection (NDA #203923), the labeling for the now discontinued product is woefully inadequate. Because an application submitted under Section 505(j) must have the same labeling as the RLD,[2] FDA approval of an ANDA referencing the U.S. Army's discontinued NDA as the RLD would result in approval of a drug product that is misbranded under the FD&C Act because its FDA-approved labeling no longer "bears . . . adequate directions for use."[3]

A. Action Requested

While Sodium Thiosulfate Injection (NDA #203923) manufactured, labeled, and released pursuant to current approval standards is unquestionably safe and effective as a treatment for acute cyanide poisoning, this Citizen Petition requests that FDA determine under 21 C.F.R. § 314.161(a)(3) that Sodium Thiosulfate Injection (NDA #020166), which was discontinued in 2004, was withdrawn from sale for reasons of safety or effectiveness. Importantly, FDA may make such a determination based on current standards and the availability of other drugs in the marketplace, even if the Agency would not have made the same determination in 2004 when NDA #020166 was discontinued by the U.S. Army. Drug products that FDA determines were withdrawn from sale for safety or effectiveness reasons are removed as "listed drugs" (or RLDs) from the FDA publication entitled *Approved Drug Products With Therapeutic Equivalence Evaluations* (known as the "*Orange Book*") under 21 C.F.R. § 314.162(a)(2). This Citizen Petition therefore requests further that FDA remove NDA #020166 as a listed drug from the

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[1] *See* Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA re: Docket No. FDA-2014-P-0916 (Nov. 4, 2014), at 4 [hereinafter "*Citizen Petition Denial*"].
[2] *See* FD&C Act § 505(j)(2)(A)(v).
[3] *See id.* § 502(f).

Orange Book and refrain from receiving or approving any ANDA that identifies Sodium Thiosulfate Injection (NDA #020166) as the RLD.

B. Statement of Grounds

Set forth below is background information regarding FDA's 1992 approval of Sodium Thiosulfate Injection (NDA #020166), as well as the drug product's placement on the *Orange Book*'s list of discontinued drug products.

1. Background

On January 16, 1991, President George H.W. Bush announced the start of what would be called Operation Desert Storm—a military operation to expel occupying Iraqi forces from Kuwait, the country Iraq had invaded and annexed months earlier. Also referred to as the Gulf War, the military campaign included more than 500,000 U.S. troops, as well as numerous coalition forces. At the time, there was a high level of concern in the United States that cyanide, which is frequently lethal, could be used against U.S. troops in a war zone or in a terrorist attack.[4] Cyanide is highly toxic in humans and can be fatal if not immediately treated with an effective antidote.[5] One of the long-standing antidote treatments for cyanide poisoning is Sodium Nitrite Injection followed immediately by Sodium Thiosulfate Injection.[6] To address this concern, the U.S. Army submitted an NDA for Sodium Thiosulfate Injection (NDA #020166), which was approved by FDA on February 14, 1992.[7]

Due to the exigent circumstances of the Gulf War, and the concern about U.S. troops being potentially subject to cyanide poisoning, the U.S. Army's NDA for Sodium Thiosulfate Injection was approved based entirely on the quality specifications contained in the then-current USP monograph. Per the drug product's approved labeling, the product—which was labeled as "Sodium Thiosulfate Injection, USP"—complied with the then-applicable USP specifications.[8] FDA accepted the then-applicable USP specifications and did not impose additional quality specifications as a condition of its approval of NDA #020166.

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[4] *See Citizen Petition Denial* at 1.
[5] *See* FDA, Notice, *Sodium Nitrite Injection and Sodium Thiosulfate Injection Drug Products Labeled for the Treatment of Cyanide Poisoning; Enforcement Action Dates*, 77 Fed. Reg. 71,006, 71,006 (Nov. 28, 2012) [hereinafter "*Enforcement Discretion Notice*"].
[6] *See Citizen Petition Denial* at 1.
[7] *See* FDA, Drugs@FDA, "Sodium Thiosulfate (NDA #020166)" (visited Mar. 10, 2022), https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020166.
[8] *See* Package Insert, *Sodium Thiosulfate Injection, USP* (Feb. 18, 1992) (attached as Exhibit "A" hereto).

The U.S. Army discontinued the distribution and use of Sodium Thiosulfate Injection (NDA #020166) on March 24, 2004. Although listed on the *Orange Book*'s Discontinued Drug Product List,[9] Sodium Thiosulfate Injection (NDA #020166) continues to appear in the *Orange Book* as a possible RLD for sodium thiosulfate injection drug products.[10] Per the *Orange Book*, FDA has not yet determined whether the product was discontinued or withdrawn for safety or effectiveness reasons.[11] Although NDA #020166 is still listed as a possible RLD for sodium thiosulfate injection products, FDA has identified Sodium Thiosulfate Injection (NDA #203923) as the Reference Standard. As a result, an ANDA applicant referencing discontinued NDA #020166 as the RLD would be required to use NDA #203923 to establish that the ANDA is bioequivalent to the RLD.[12]

2. FDA Should Determine That Sodium Thiosulfate Injection (NDA #020166) Was Withdrawn from Sale for Reasons of Safety or Effectiveness

This Citizen Petition hereby requests that FDA determine that the U.S. Army's NDA #020166 was discontinued for safety or effectiveness reasons. Any person may petition FDA to determine (or the Agency may determine on its own) that a listed drug was withdrawn from sale for reasons of safety or effectiveness.[13] This determination may be made at any time after the drug has been withdrawn from sale, but it must be made before the Agency approves an ANDA that references the discontinued drug as the listed drug.[14] Furthermore, FDA may not approve an ANDA that does not refer to a listed drug.

For the following reasons, FDA should determine that the U.S. Army's Sodium Thiosulfate Injection (NDA #020166) was discontinued for safety or effectiveness reasons:

First, while NDA #203923 would serve as the Reference Standard for an ANDA referencing the U.S. Army's discontinued NDA as the RLD, that designation only has relevance for bioequivalence testing. As FDA has made clear, an ANDA applicant must compare its

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[9] *See* FDA, *Approved Drug Products With Therapeutic Equivalence Evaluations* 6-411 (42nd ed. 2022) [hereinafter "*Orange Book*"].
[10] *See id.* (search results for "sodium thiosulfate").
[11] *Compare id.* § 1.11 (stating that "drug products in the discontinued section of the *Orange Book* (Discontinued Drug Product List) for which a determination has been made that the products were not withdrawn for safety or effectiveness reasons have been annotated with a footnote" that says "*Federal Register* determination that product was not discontinued or withdrawn for safety or effectiveness reasons"), *with id.* at 6-411 (entry for Sodium Thiosulfate (N020166) on Discontinued Drug Product List is *not* annotated with a footnote).
[12] *See* FDA, Guidance for Industry, *Referencing Approved Drug Products in ANDA Submissions* § III(C)(1) (Oct. 2020) [hereinafter "*RLD Guidance*"].
[13] *See* 21 C.F.R. § 314.161(b) ("Any person may petition [FDA] . . . for a determination whether a listed drug has been voluntarily withdrawn for safety or effectiveness reasons.").
[14] *See id.* § 314.161(a).

proposed formulation and labeling to the RLD, not to the Reference Standard.[15] Importantly, as noted above, the proposed labeling in an ANDA must be the same as the labeling of the RLD (with limited exceptions not relevant here).[16]

Second, the U.S. Army's discontinued NDA #020166 was approved in 1992 based entirely on the then-applicable USP specifications. Those quality specifications, although acceptable at the time of approval, do not reflect the current quality standards for sodium thiosulfate drug substance or drug product. Indeed, even the current USP monographs reflect only minimum quality requirements that, by themselves, cannot assure adequate product quality. Referring to the USP specifications applicable in 2014, FDA acknowledged: "We agree that the quality specifications in the official USP drug product and drug substance monographs related to . . . sodium thiosulfate *are minimum requirements, but not sufficient, to ensure adequate product quality*."[17] At the same time, the Agency has stated that for sodium thiosulfate drug products, "the adequacy of their chemistry, manufacturing and control specifications" is critical to assuring "quality, safety, and efficacy."[18] To that end, the Agency further stated:

> "*Commodity substances, such as ...sodium thiosulfate, generally are not manufactured under current good manufacturing practices (cGMPs) and must be purified under cGMPs after they are purchased from the supplier . . . , FDA generally requires that specifications include tests and acceptance criteria to account for the lack of regulatory controls in the manufacture of the drug substances*".[19]

If someone today began manufacturing and distributing Sodium Thiosulfate Injection in accordance with the quality standards contained in NDA #020166, then the quality, safety, and efficacy of the drug substance and drug product could not be assured. In fact, under Section 501 of the FD&C Act, a Sodium Thiosulfate Injection drug product that is consistent with NDA #020166 would be considered adulterated because its quality and purity characteristics would not conform to current standards.[20] FDA therefore should determine that Sodium Thiosulfate Injection (NDA #020166), a drug product that by today's standards could not be lawfully marketed, was discontinued for safety or effectiveness reasons.

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[15] *See RLD Guidance* § III(C)(1) (stating that "even if FDA selects a reference standard that is a drug product other than the RLD for use in conducting in vivo bioequivalence studies, an ANDA applicant must demonstrate that its proposed generic drug meets the sameness requirements in section 505(j) of the FD&C Act and Agency regulations in relation to the RLD").
[16] *See* FD&C Act § 505(j)(2)(A)(v).
[17] *Citizen Petition Denial* at 4 (emphasis added). Moreover, even though the USP specifications for sodium thiosulfate have been significantly updated and enhanced since 1992, they are still, by themselves, insufficient.
[18] *Enforcement Discretion Notice*, 77 Fed. Reg. at 71,007.
[19] *Citizen Petition Denial* at 4 n,10.
[20] *See* FD&C Act § 501(a)(2)(B).

On June 18, 2014, FDA received a Citizen Petition that asked the Agency to refrain from receiving or approving any ANDA for any sodium thiosulfate drug product unless the proposed quality and purity specifications are the same as or more stringent than the specifications in NDA #203923.[21] To be clear, this Citizen Petition is not asking for FDA to require ANDAs for sodium thiosulfate drug products to meet the identical quality specifications in NDA #203923 in order to obtain FDA approval of a generic drug product. Instead, this Citizen Petition merely references the 2014 petition and incorporates the information contained in it to illustrate the dramatic difference between the quality and purity specifications required by NDA #203923 compared to those required for discontinued NDA #020166.

Third, as noted above, the labeling for discontinued NDA #020166 is now 30 years old and, when compared to the labeling for NDA #203923, it is abundantly clear that the labeling for the discontinued product is woefully inadequate.[22] Below, please find a table that identifies several critical differences in the labeling of NDA #020166 and NDA #203923.

Table 1. Comparison of Labeling of NDA #020166 and NDA #203923.

Labeling Section	NDA #020166	NDA #203923	Comments
Indication	"*Sodium thiosulfate injection when used in conjunction with sodium nitrite is indicated for the treatment of cyanide poisoning.*"	"*Sodium Thiosulfate Injection is indicated for sequential use with sodium nitrite for the treatment of acute cyanide poisoning that is judged to be serious or life-threatening. When the diagnosis of cyanide poisoning is uncertain, the potential risks associated with Sodium Thiosulfate Injection should be carefully weighed against the potential benefits, especially if the*	In NDA #203923, FDA restricted use to serious or life-threatening cases of acute cyanide poisoning.

[21] *See* Citizen Petition, Docket No. FDA-2014-P-0916 (June 18, 2014), at 1.
[22] *Compare* Exhibit "A" (FDA-approved labeling for the U.S. Army's discontinued NDA #020166), *with* Exhibit "B" (FDA-approved labeling for NDA #203923).

Labeling Section	NDA #020166	NDA #203923	Comments
		patient is not in extremis."	
Administration	"*Even though the diagnosis is doubtful, the therapy recommended should be instituted immediately.*"	"*If clinical suspicion of cyanide poisoning is high, administer Sodium Thiosulfate Injection without delay.*"	In NDA #203923, FDA did not approve administration if diagnosis is doubtful.
	No text	"*Administration of sodium nitrite and sodium thiosulfate should be considered adjunctive to appropriate supportive therapies. Airway, ventilatory and circulatory support, and oxygen administration should not be delayed in order to administer sodium nitrite and sodium thiosulfate.*"	In NDA #203923, FDA emphasized clinical attention to supporting vital functions before administering antidotes.
	"*Even if the patient seems perfectly well, the medication may be given for prophylactic purposes 2 hours after the first injections.*"	No text	In NDA #203923, FDA did not approve prophylactic use of cyanide antidotes.
Adverse Reactions Use in Specific Populations Drug Interactions Pregnancy and Lactation Risk Summaries Overdosage	No text	Information included	In NDA #203923, FDA mandated inclusion of important safety information.

The safe usage of Sodium Thiosulfate Injection that is labeled in accordance with NDA #020166 cannot be assured because of the lack of important safety information and potentially dangerous administration instructions, as identified in Table 1. Because an application submitted under Section 505(j) of the FD&C Act must have the same labeling as the RLD,[23] approving an ANDA referencing NDA #020166 as the RLD would necessarily result in a drug product that is misbranded, since its labeling would be false or misleading and would not bear "adequate directions for use."[24] FDA therefore should determine that the U.S. Army's Sodium Thiosulfate Injection (NDA #020166), a drug product that would be considered misbranded under current standards, was discontinued for reasons of safety or effectiveness.

Finally, in determining whether an older formulation of a drug product has been discontinued for safety or efficacy reasons, FDA may look to the availability of a more recently approved version of the drug product. In that regard, the action petitioner seeks is analogous to the action FDA took for Oxycontin (oxycodone hydrochloride). In 2013, FDA determined that the original formulation of Oxycontin had been withdrawn from sale for reasons of safety or effectiveness after a new, reformulated version of Oxycontin with abuse-deterrent properties was

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[23] *See* FD&C Act § 505(j)(2)(A)(v). In draft guidance issued in 2016, FDA suggested that an ANDA need not have the same labeling as the RLD when the RLD has been discontinued and its labeling is out of date or otherwise inaccurate. *See* FDA, Draft Guidance, *Updating ANDA Labeling After the Marketing Application for the Referenced Listed Drug Has Been Withdrawn* § I (July 2016) [hereinafter "*Withdrawn RLD Draft Guidance*"]. While that is certainly the case for an ANDA approved before the RLD was discontinued, it is not the case for an ANDA that was submitted or pending after the RLD was discontinued. Specifically, as part of the Food and Drug Administration Amendments Act of 2007 ("FDAAA"), FDA was given explicit authority to require certain labeling changes to an approved ANDA whose RLD is no longer marketed. *See* FD&C Act 505(o)(4). The FDAAA provision in question, however, applies only to approved ANDAs. It did not change the statutory requirement that an ANDA cannot be approved unless it has the same labeling as the RLD at the time of approval. *See id.* § 505(j)(2)(A)(v).

The *Withdrawn RLD Draft Guidance* further suggests that when the RLD has been discontinued, an ANDA applicant should look at the labeling of any actively marketed drugs containing the same active ingredient as a guide for the labeling it should submit with its ANDA. *See Withdrawn RLD Draft Guidance* § II. That suggestion is inconsistent with FDA's acknowledgement in the *RLD Guidance* that when an ANDA applicant must use a different drug as the Reference Standard – e.g., when the RLD has been discontinued – it must still look to the RLD (and not the Reference Standard) to satisfy the statutory sameness requirements, which as explained above requires the same labeling. *See RLD Guidance* § III(C)(1). More importantly, it is impossible to square such advice with the statutory requirement that, to be approved, an ANDA must have the same labeling as the RLD. *See* FD&C Act § 505(j)(2)(A)(v). Indeed, if an ANDA applicant must use a different drug than the RLD for both labeling and bioequivalence purposes, then it should be required to use that drug—not the discontinued drug—as the RLD.

A draft guidance document does not reflect FDA's current thinking until finalized, and even when finalized a guidance document is legally nonbinding and cannot supersede a statutory requirement. The *Withdrawn RLD Draft Guidance* therefore cannot supersede the FD&C Act's statutory approval requirements. Moreover, Congress had the opportunity to exempt ANDAs from the "same labeling" requirement under Section 505(j)(2)(A)(v) of the FD&C Act when it created the Suitability Petition process, but it declined to do so. Under the Suitability Petition process, an ANDA applicant can ask FDA for permission to submit an ANDA that differs from the RLD in several specific ways. *See* FD&C Act 505(j)(2)(C). While those differences from the RLD include different strengths and different dosage forms, they do not include different labeling. *See id.*

[24] *See* FD&C Act § 502(f).

approved by the Agency. Accordingly, the Agency removed original Oxycontin from the list of drug products published in the *Orange Book* and said that it would not accept or approve ANDAs that referenced original Oxycontin.[25] Instead, FDA directed ANDA applicants to look to the new version as the RLD. Here, the petitioner is asking FDA to determine that a version of Sodium Thiosulfate Injection approved under exigent circumstances, with quality specifications and labeling that by current standards are insufficient and inadequate, was discontinued for safety or effectiveness reasons after a new version, approved with updated quality specifications and labeling, has been approved and become available.

3. Conclusion

This Citizen Petition asks FDA to determine that the U.S. Army's Sodium Thiosulfate Injection (NDA #020166) was discontinued for safety or effectiveness reasons, such that Sodium Thiosulfate Injection (NDA #020166) must be removed from the *Orange Book* as a possible RLD for an ANDA seeking approval for a generic drug product. Once removed from the *Orange Book* as a possible RLD for sodium thiosulfate drug products, ANDA sponsors will not be able to reference the obsolete quality specifications or inadequate labeling of NDA #020166. Instead of referencing NDA #020166 as the RLD and NDA #203923 as the Reference Standard, a sponsor of a future ANDA for a generic sodium thiosulfate drug product would reference NDA #203923 as both the RLD and Reference Standard.

C. Environmental Impact

An environmental assessment report on the action requested in this petition is not required under 21 C.F.R. § 25.31(a) and (g).

D. Certification

Section 505(q) and, therefore, the certification requirement found therein, does not apply to this citizen petition. As FDA is aware, Section 505(q)(1)(A) specifically references pending applications. Because the provision is concerned with the possibility that the approval of a pending application could be delayed by issues raised in a petition, FDA has explained that Section 505(q) "appl[ies] only to petitions for which, at the time the petition is submitted, at least one ANDA, 505(b)(2) application, or 351(k) application related to the subject matter of the petition is

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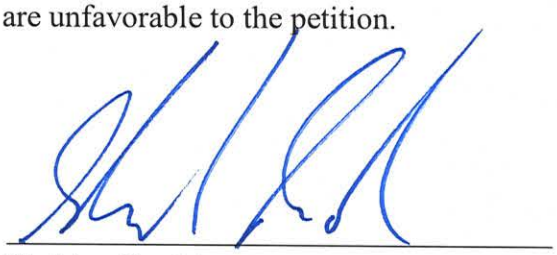
[25] *See* FDA, Notice, *Determination That the OXYCONTIN (Oxycodone Hydrochloride) Drug Products Covered by New Drug Application 20–553 Were Withdrawn From Sale for Reasons of Safety or Effectiveness*, 78 Fed. Reg. 23,273 (Apr. 18, 2013).

pending."[26] We know that no application referencing the Army's discontinued NDA is pending at FDA because, pursuant to FDA's regulations, the sponsor of such an ANDA is required to simultaneously submit a petition to FDA asking the agency to make a formal determination concerning whether the discontinued RLD was withdrawn for safety or efficacy reasons.[27] No such petition is on file at www.regulations.gov, meaning that no application referencing the U.S. Army's discontinued NDA as the RLD has been submitted to (and, therefore, is pending at) the Agency.

While 21 C.F.R. § 10.31, when applicable, also contains a certification requirement, that section also does not apply to this citizen petition. Specifically, Section 10.31 applies only when the requested action could delay the approval of an ANDA under Section 505(j) of the FD&C Act. FDA's agreement to take the action requested by this petition, however, would not delay the approval of an ANDA under Section 505(j) because FDA (whether or not it receives this petition) is required to determine whether a discontinued drug product was withdrawn for safety or efficacy reasons before it can approve an ANDA referencing the drug as the RLD.[28]

Based on the above, we include only the certification required by 21 C.F.R. § 10.30:

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



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[26] FDA, Guidance for Industry, *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act* § III(A)(3) (Sep. 2019).
[27] *See* 21 C.F.R. § 314.122(a).
[28] *See* FD&C Act § 314.161(a).