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VIA ELECTRONIC SUBMISSION

Division of Dockets Management
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane (HFA-305)
Rockville, MD 20852

Citizen Petition

The undersigned ("Petitioner") submits this Citizen Petition pursuant to the Federal Food, Drug and Cosmetic Act ("FD&C Act") and in accordance with 21 C.FR. § 10.25(a) and 21 C.FR. § 10.30 with regard to the FDA-designated Reference Standard ("RS") for Dextromethorphan Hydrobromide and Promethazine Hydrochloride Oral Syrup, 15 mg/5 mL; 6.25 mg/5 mL. The current RS, approved under Abbreviated New Drug Application ("ANDA") 040649 is commercially unavailable. For this reason, the undersigned requests that the Food and Drug Administration ("FDA") take action to maintain a pathway for ANDA submissions for Dextromethorphan Hydrobromide and Promethazine Hydrochloride Oral Syrup, 15 mg/5 mL; 6.25 mg/5 mL. Specifically, Petitioner requests that FDA amend the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") to designate Dextromethorphan Hydrobromide and Promethazine Hydrochloride Oral Syrup, 15 mg/5 mL; 6.25 mg/5 mL, approved under ANDA 088864 and which is currently commercially available, as an additional alternate (or a new) RS for the drug.

A. ACTION REQUESTED

Petitioner requests that FDA designate ANDA 088864 (Dextromethorphan Hydrobromide and Promethazine Hydrochloride Oral Syrup, 15 mg/5 mL; 6.25 mg/5 mL) held by Wockhardt Bio AG ("Workhardt") as a RS for purposes of FDA evaluation of ANDAs for Dextromethorphan Hydrobromide and Promethazine Hydrochloride Oral Syrup, 15 mg/5 mL; 6.25 mg/5 mL.

B. STATEMENT OF GROUNDS

FD&C Act § 505(j) allows the marketing of generic versions of previously approved drug products when the generic drug product is the subject of an ANDA. To obtain ANDA approval, the ANDA applicant must show, among other things, that with respect to a listed drug (*i.e.*, a

previously approved drug product), the generic drug product has the same active ingredient(s) in the same strength, dosage form and route of administration, has essentially identical labeling, and is bioequivalent.

A "listed drug" includes a new drug product that has an effective approval under FD&C Act § 505(j), that has not been withdrawn or suspended under FD&C Act § 505(e)(1) - (5) or (j)(6), and that has not been withdrawn from sale for reasons of safety or effectiveness. *See* 21 C.F.R. § 314.3. Listed drugs are identified in FDA's Orange Book. An RLD is the listed drug identified by FDA as the drug product on which an ANDA applicant should rely in seeking approval of an application.

A "reference standard," designated as "RS" in the Orange Book, is the product that an ANDA applicant must use to conduct in vivo bioequivalence testing, if required, for approval. *In vivo* bioequivalence evidence is not required in all circumstances, especially in the instances where bioequivalence is self-evident, and *in vitro* studies may be conducted to support demonstration of bioequivalence. *See* 21 C.F.R. § 320.22 and 320.24(b)(6). However, where "there are limited or no quantities of the reference standard in distribution" a potential ANDA applicant may request designation of a new RS through the submission of a citizen petition. *See Referencing Approved Drug Products in ANDA Submissions, Draft Guidance for Industry* (January 2017) at p. 9. FDA will typically select as a new RS a drug product that is therapeutically equivalent to the RLD and the market leader. FDA may also consider other factors that may "make the development process more efficient." *Id.* at p. 9.

Indeed, FDA has previously designated a new RS when the listed RS was commercially unavailable. For instance, in response to a Citizen Petition filed by Aurobindo Pharma USA, FDA designated a new RS for phenoxybenzamine hydrochloride capsules, USP, 10 mg, because the previously designated RS was commercially unavailable.

> We have examined the issues presented in your Petition and have determined that you have stated grounds for FDA to select phenoxybenzamine hydrochloride capsules, USP 10 mg, approved under ANDA 204522 held by Par, as a reference standard. We agree that Dibenzyline is no longer available in the market. In this instance, based on the available information, it is appropriate to select phenoxybenzamine hydrochloride capsules, USP 10 mg, approved under ANDA 204522, as the new reference standard because it is therapeutically equivalent to Dibenzyline (phenoxybenzamine hydrochloride) Capsules, 10 mg (Dibenzyline), approved under NDA 008708, and it is the current market leader as determined by FDA on the basis of commercial data.

Docket No. FDA-2019-P-1607, Decision dated December 13, 2019 at pp. 2-3. Similarly, in response to a Citizen Petition filed in March 2018, FDA designated a new RS for naproxen oral suspension, 25 mg/mL because the previously listed RS was "unavailable in the market or [was] available in such limited quantities that a potential ANDA applicant may not be able to obtain

sufficient quantities of the RS to conduct in vivo bioequivalence testing." Docket No. FDA-2018-P-1195, Decision dated May 08, 2019 at pp. 2-3.

Here, the original RLD for Dextromethorphan Hydrobromide and Promethazine Hydrochloride Oral Syrup, 15 mg/5 mL; 6.25 mg/5 mL (NDA 011265), was discontinued or withdrawn from the market for reasons other than safety or efficacy reasons. Currently, the only RS is Dextromethorphan Hydrobromide and Promethazine Hydrochloride Oral Solution, 15 mg/5 mL; 6.25 mg/5 mL approved under ANDA 040649. Despite diligent efforts to obtain sufficient quantities of the current RS—Promethazine DM Oral Solution (Dextromethorphan Hydrobromide and Promethazine Hydrochloride Oral Solution, 15 mg/5 mL; 6.25 mg/5 mL) approved under ANDA 040649—the drug product is not commercially available. Therefore, Promethazine DM Oral Solution, approved under ANDA 040649, cannot be obtained for developmental purposes and to establish pharmaceutical equivalence. As a result, Promethazine DM Oral Solution is shielded from additional generic competition. Similar to the aforementioned decisions in Docket Nos. FDA-2019-P-1607 and FDA-2018-P-1195, in an effort to introduce additional generic competition, FDA should designate Dextromethorphan Hydrobromide and Promethazine Hydrochloride Oral Syrup, 15 mg/5 mL; 6.25 mg/5 mL, approved under ANDA 088864 and commercially available, as a RS.

There is a sound basis for Dextromethorphan Hydrobromide and Promethazine Hydrochloride Oral Syrup, 15 mg/5 mL; 6.25 mg/5 mL, approved under ANDA 088864 as a new RS. The proposed new RS, Dextromethorphan Hydrobromide and Promethazine Hydrochloride Oral Syrup, 15 mg/5 mL; 6.25 mg/5 mL, approved under ANDA 088864 held by Wockhardt, appears to lead the U.S. market in terms of number of units sold (as per IMS data), and should therefore be more readily accessible and more appropriate for RS designation.

Accordingly, the undersigned requests that FDA designate in the Orange Book Dextromethorphan Hydrobromide and Promethazine Hydrochloride Oral Syrup, 15 mg/5 mL; 6.25 mg/5 mL, approved under ANDA 088864, as a new RS.

C. ENVIRONMENTAL IMPACT

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

D. ECONOMIC IMPACT

In accordance with 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition. Petitioner hereby commits to promptly provide this information, if so requested.

E. CERTIFICATION

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 is unfavorable to the petition.

Sincerely,

Frank D. Rodriguez