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BY ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Citizen Petition

The undersigned ("Petitioner") submits this Citizen Petition pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act ("FDC Act"), and in accordance with 21 C.F.R. §§ 10.20 and 10.30, to request that the Food and Drug Administration ("FDA") amend the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") to designate Neostigmine Methylsulfate Injection Solution, approved under New Drug Application ("NDA") 203629, as both a Reference Listed Drug ("RLD") and a Reference Standard ("RS").

I. ACTION REQUESTED

Petitioner requests that FDA designate NDA 203629 (Neostigmine Methylsulfate Injection Solution) as both a RLD and a RS for purposes of FDA evaluation of Abbreviated New Drug Applications ("ANDAs") for Neostigmine Methylsulfate Injection Solution.

II. STATEMENT OF GROUNDS

FDC Act § 505(j) allows the marketing of generic versions of previously approved drug products based on FDA approval of an ANDA. To obtain ANDA approval, the 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A "listed drug" includes a new drug product that has an effective approval under FDC Act § 505(j), that has not been withdrawn or suspended under FDC Act §§ 505(e)(1) through (5) or (j)(5), and that has not been withdrawn from sale for reasons of safety or effectiveness.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. The product designated by FDA as the "reference standard" in the Orange Book must be used to conduct the in vivo bioequivalence testing required for FDA approval. *See generally* FDA, *Draft Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions*, at 9 (Jan. 2017) ("RLD/RS Guidance").

FDA initially stated its policy for designating RLDs in the preamble to the Agency's 1992 final ANDA Regulations. Specifically, in response to comments asking FDA to explain how the Agency determines which drugs should be RLDs, FDA stated:

> FDA will designate [RLDs]. Generally, the [RLD] will be the NDA drug product for a single source drug product. For multiple source NDA drug products or multiple source drug products without an NDA, the [RLD] generally will be the market leader as determined by FDA on the basis of commercial data. FDA recognizes that, for multiple source products, a product not designated as the listed drug and not shown bioequivalent to the listed drug may be shielded from direct generic competition. If an applicant believes that there are sound reasons for designating another drug as a [RLD], it should consult FDA.

FDA, Final Rule, ANDA Regulations, 57 Fed. Reg. 17,950, 17,958 (Apr. 28, 1992). In addition, FDA states in the preface to the Orange Book that:

> In some instances when FDA has not designated a listed drug as a [RLD], such listed drug may be shielded from generic competition. If FDA has not designated a [RLD] for a drug product the applicant intends to duplicate, the potential applicant ***may*** submit a controlled correspondence to the Office of Generic Drugs to ask FDA to designate a reference listed drug for that drug product.

Orange Book Preface at x (40th ed. 2020) (emphasis added); *see also* RLD/RS Guidance at 5 ("If FDA has not designated an RLD for a drug product the applicant intends to duplicate, the potential applicant ***may*** submit controlled correspondence to FDA asking FDA to designate an RLD for that drug product") (emphasis added).

With respect to RS designation, FDA has stated: "If there is no reference standard in the Active Section of the Orange Book for a drug product the applicant intends to duplicate, the potential applicant ***may*** submit controlled correspondence to FDA asking FDA to select a reference standard for that drug product." RLD/RS Guidance at 9 (emphasis added).

There is a sound basis for designating NDA 203629 as both a RLD and a RS: Neostigmine Methylsulfate Injection Solution, approved in three strengths—*i.e.*, 3 mg/3 mL (1 mg/mL), 5 mg/10 mL (0.5 mg/mL), and 10 mg/10 mL (1 mg/mL)—is a single-source product, and without RLD and RS designations, NDA 203629 is unnecessarily shielded from generic competition.

Petitioner acknowledges that both the RLD/RS Guidance and Orange Book Preface suggest that the submission of controlled correspondence for RLD and RS designations for Neostigmine Methylsulfate Injection Solution is an appropriate mechanism to obtain such designations; but FDA's use of the word "may" in both documents makes clear that controlled correspondence is not the exclusive mechanism to obtain such designations. Indeed, in April 2019, a citizen petition (Docket No. FDA-2019-P-1636) was submitted to FDA requesting that the Agency designate Neostigmine Methylsulfate Injection Solution approved under NDA 203629 as a RLD. Because of the related content and request of that citizen petition, Petitioner believes a citizen petition is appropriate in this case and that the related petitions should be ruled on together.

III. ENVIRONMENTAL IMPACT

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

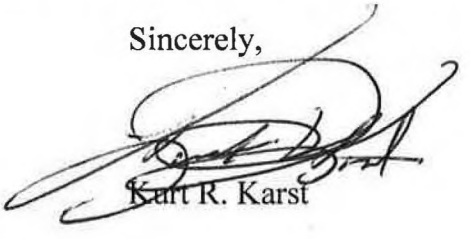
IV. ECONOMIC IMPACT

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.

V. CERTIFICATION

Petitioner certifies that, to the best knowledge and belief of Petitioner, 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,



Kurt R. Karst

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