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May 8, 2020

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 the Federal Food, Drug, and Cosmetic Act ("FDC Act") and in accordance with 21 C.F.R. §§ 10.25(a) and 10.30 with regard to the FDA-designated Reference Standard ("RS") for Pyrimethamine Tablets, 25 mg. The current RS, approved under New Drug Application ("NDA") 008578, is commercially unavailable. For this reason, Petitioner requests that the Food and Drug Administration ("FDA") take action to maintain a pathway for Abbreviated NDA ("ANDA") submissions. Petitioner requests that FDA designate an additional (or new) RS for Pyrimethamine Tablets, 25 mg, and amend the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") to reflect ANDA 207127 as a RS for the drug.

I. ACTION REQUESTED

Petitioner requests that FDA designate ANDA 207127 (Pyrimethamine Tablets, 25 mg) held by Cerovene, Inc. ("Cerovene") as a RS for purposes of FDA evaluation of ANDAs for Pyrimethamine Tablets, 25 mg. Petitioner further requests that FDA expedite a response to this petition so that bioequivalence studies can be conducted and an ANDA can be submitted to FDA.

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A "listed drug" includes a new drug product that has an effective approval under FDC Act § 505(j), that has not been withdrawn or suspended under FDC Act §§ 505(e)(1) through (5) or (j)(5), and that has not been withdrawn from sale for reasons of safety or effectiveness.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. However, where there is a "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. FDA, *Draft Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions*, at 9 (Jan. 2017).

Despite diligent efforts to obtain sufficient quantities of the present RS— DARAPRIM (pyrimethamine) Tablets, 25 mg (NDA 008578)—the drug product is not commercially available because of a restricted distribution program the NDA holder has established on its own initiative. As such, Pyrimethamine Tablets, 25 mg, is shielded from additional generic competition. In an effort to introduce further competition, FDA should promptly designate Cerovene ANDA 207127—the only approved generic version of DARAPRIM listed in the Orange Book (below)—as the new (or an additional) RS for Pyrimethamine Tablets, 25 mg.

PYRIMETHAMINE						
TABLET;ORAL						
DARAPRIM						
AB	+!	VYERA PHARMS LLC	25MG		N008578	001
PYRIMETHAMINE						
AB		CEROVENE INC	25MG		A207127	001 Feb 28, 2020

There is a sound basis for selecting an ANDA 207127 as a new RS. As FDA noted when approving ANDA 207127:

> [C]ertain "gaming" tactics have been used at times to delay generic competition. One example is when brand-name drug manufacturers attempt to prevent potential generic applicants from obtaining samples of certain medicines necessary to support approval of a generic drug application. To improve transparency about this issue, the FDA posted a list identifying all drugs for which the FDA has received an inquiry related to limited distribution of the reference drug from a prospective generic applicant. Daraprim is on this list.

FDA, Press Release, FDA Approves First Generic of Daraprim (Feb. 28, 2020), available at https://www.fda.gov/news-events/press-announcements/fda-approves-first-generic-daraprim.

Although a single generic version of DARAPRIM is now approved, access to DARAPRIM sample to conduct the bioequivalence studies and other testing recommended by FDA, see FDA, Draft Guidance on Pyrimethamine (Mar. 2015), available at

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Pyrimethamine_oral%20tab_008578_RC03-15.pdf, remains problematic as a result of the "DARAPRIM Direct Program" established by Vyera Pharmaceuticals, LLC, the holder of NDA 008578. Under that restricted distribution program, drug product procurement by a potential generic drug manufacturer is significantly hampered. Indeed, FDA's now-defunct list of "Reference Listed Drug (RLD) Access Inquiries" identified DARAPRIM as a drug about which "FDA has received numerous inquiries from prospective generic applicants indicating that they would like to develop a generic version of a marketed drug, but are unable to obtain the necessary samples of the [RLD] because the RLD is subject to limited distribution." FDA, Reference Listed Drug (RLD) Access Inquiries (updated Sept. 24, 2019), available at https://web.archive.org/web/20191118201910/http://www.fda.gov/drugs/abbreviated-new-drug-application-anda/reference-listed-drug-rld-access-inquiries.

Accordingly, the undersigned requests that FDA designate in the Orange Book Pyrimethamine Tablets, 25 mg, approved under ANDA 207127 as a new RS.

III. ENVIRONMENTAL IMPACT

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

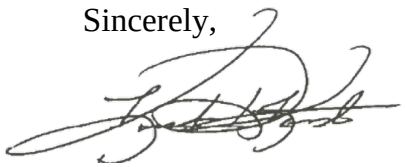
IV. ECONOMIC IMPACT

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