August 21, 2020

To,

Office of Generic Drugs (HFD-600)

Center for Drug Evaluation and Research

Food and Drug Administration

Central Document Room, 5901B

Ammendale Road, Beltsville, MD 20705

CITIZEN PETITION

Dear Sir / Madam,

The undersigned submits this citizen petition electronically under Section 505(j) of the Federal Food Drug, and Cosmetic Act and 21 CFR 10.20, 10.30 and 314.93, to request the Food and Drug Administration to designate a suitable reference standard (RS) for purpose of submitting an ANDA application for Metformin hydrochloride extended-release tablets 750 mg with reference to the current electronic orange book database (Approved Drug Products with Therapeutic Equivalence Evaluation).

The request is being made on following grounds;

1. Current Orange Book lists one reference listed drug (RLD) GLUCOPHAGE® XR (metformin hydrochloride) extended-release tablets, for oral use, NDA # 021202 of EMD SERONO INC which is listed as 'Discontinued' (not discontinued or withdrawn for safety or efficacy reasons) and one generic product Metformin hydrochloride extended-release tablets 750 mg, ANDA # A078596 of Amneal Pharmaceuticals NY LLC is listed as reference standard (RS). Though "Metformin hydrochloride extended-release tablets 750 mg, ANDA # A078596 by Amneal Pharmaceuticals NY LLC." is not listed as discontinued in Electronic Orange Book but is currently unavailable in the US market. **COMPANY ANNOUNCEMENT communication** by Amneal Pharmaceuticals LLC Issue Voluntary Nationwide Recall of Metformin Hydrochloride Extended Release Tablets, USP, 500 mg and 750 mg is provided as evidence for same.

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2. Approved Generic listed product tabulated below which are not discontinued as per the Orange Book, eligible to be designated as reference standard due to unavailability of the current Metformin hydrochloride extended-release tablets 750 mg, ANDA # A078596 by Amneal Pharmaceuticals NY LLC".

Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book) database Current through August 14, 2020 is provided in following table;

Approved Generic listed product

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
DISCN	METFORMIN HYDROCHLORIDE	GLUCOPHAGE XR	N021202	TABLET, EXTENDED RELEASE	ORAL	750MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**		RLD		EMD SERONO INC
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	A076869	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			ACTAVIS LABORATORIES FL INC
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	A206145	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			ALKEM LABORATORIES LTD
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	A078596	TABLET, EXTENDED RELEASE	ORAL	750MG	AB		RS	AMNEAL PHARMACEUTICALS NY LLC
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	A079118	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			AUROBINDO PHARMA LTD
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	A207427	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			BEXIMCO PHARMACEUTICALS USA INC
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	A077078	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			CADILA HEALTHCARE LTD
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	A078321	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			CSPC OUYI PHARMACEUTICAL CO LTD
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	A209313	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			GRANULES INDIA LTD

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RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	**A202306**	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			INTELLIPHARMACEUTICS CORP
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	**A090295**	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			MARKSANS PHARMA LTD
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	**A076756**	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			NOSTRUM PHARMACEUTICALS LLC
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	**A208880**	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			PRINSTON PHARMACEUTICAL INC
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	**A077336**	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			SUN PHARMACEUTICAL INDUSTRIES LTD
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	**A076864**	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			TEVA PHARMACEUTICALS USA INC
RX	METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE	**A211052**	TABLET, EXTENDED RELEASE	ORAL	750MG	AB			YICHANG HUMANWELL PHARMACEUTICAL CO LTD

* Data accessed on August 14, 2020

A. Action Requested

Macleods Pharmaceuticals Limited requests the Food and Drug Administration (FDA) to designate the suitable RS from the **Approved Generic listed product** tabulated above, upon which ANDA applicant can rely for purpose of ANDA filing bioequivalence demonstration as per **product specific guidance bio-recommendation**.

B. Statement of Grounds

The Food and Drug Administration maintains a list of drug products, which are eligible for submission as Abbreviated New Drug Applications (ANDA's) in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (The Orange Book).

FDC 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 application sponsor must show, among other things, that with respect to a listed drug (i.e., a previously approved drug

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product), the generic drug product has the same active ingredient(s) in the same strength, has essentially identical labeling.

Due to market unavailability of designated reference listed drug and reference standard, evaluation/comparison of a Macleod's generic drug could not be executed. In view of the draft guidance "***Referencing Approved Drug Products in ANDA submissions***", *January 2017 ; III C Reference Standard*, wherein the event of the Agency selecting a new reference standard, citation.....If there is a reference standard in the Active Section of the Orange Book but there are limited or no quantities of the reference standard in distribution, or a potential ANDA applicant believes a reference standard other than the one selected by FDA is appropriate, then the potential applicant may submit a citizen petition under 21 CFR 10.25(a) and 10.30 to request that FDA select that different listed drug also as a reference standard.

The Petitioner (Macleods) therefore respectfully requests FDA to designate suitable RS from the Approved Generic listed product tabulated above, upon which ANDA applicant can rely for purpose of ANDA filing bioequivalence demonstration as per product specific guidance bio-recommendation, as FDC 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.

In support of our request, we have included the following data;

1. **Current Orange Book Search Results listing**:
    a) Approved generic products which are not discontinued
    b) Reference listed drug
    c) Reference standard
    d) Approved generic products which are discontinued
2. **COMPANY ANNOUNCEMENT communication** by Amneal Pharmaceuticals LLC Issuing Voluntary Nationwide Recall of Metformin Hydrochloride Extended Release Tablets, USP, 500 mg and 750 mg who is a reference standard holder and distributor.

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C. Environmental Impact

The Petitioner claims a categorical exclusion from the requirement of an environmental assessment or environmental impact statement pursuant to 21 CFR § 25.31(a) and 25.15(d).

D. Economic Impact Statement

Information on the economic impact of the action requested by this Citizen Petition will be submitted if requested by FDA.

E. Certification

Macleods Pharmaceuticals Limited certifies, that to the best of knowledge and belief, this petition includes all information upon which this petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to this petition.

Sincerely,

Pooja Kulkarni,
GM, Regulatory Affairs
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