zydus pharmaceuticals

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DEC 11 '20 PM12:04

**November 30, 2020**

*To,*
*Division of Docket management*
*Food and Drug Administration*
*Department of Health and Human Services,*
*5630, Fisher Lane, Room 1061 (HFA -305)*
*Rockville, MD 20852*

**Citizen Petition**

The undersigned ("petitioner") submits this citizen petition pursuant to Federal Food, Drug and Cosmetic Act ("FD&C Act") and in accordance with 21 C.F.R. § 10.25 (a) and 10.30 to request Food and Drug Administration ("FDA") to designate Reference Listed Drug ("RLD") and Reference Standard ("RS") for Dexamethasone tablets, 1 mg and 2 mg for purpose of submitting an abbreviated new drug application ("ANDA") for Dexamethasone tablets, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg and 6 mg. As per the current *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"), DECADRON (dexamethasone) tablets, 0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 4 mg and 6 mg (NDA # 011664) held by Merck and Co Inc. is listed as RLD, which was discontinued. As per Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons. As per the current Orange Book, Dexamethasone tablets, 6 mg (ANDA # 088316) of Hikma Pharmaceuticals USA Inc.' listed as current RS for conducting the bioequivalence studies.

## I. ACTION REQUESTED

Petitioner respectfully requests FDA to designate ANDA 088306 (Dexamethasone tablets, 1 mg) and ANDA 087916 (Dexamethasone tablets, 2 mg) held by Hikma Pharmaceuticals USA Inc. ("Hikma") as both a RLD and a RS for purposes of FDA evaluation of ANDA for Dexamethasone tablets, 1 mg and 2 mg.

## 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

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same strength, dosage form and route of administration, has essentially identical labelling, and is bioequivalent.

A "listed drug" includes a new drug product that has been an effective approval under FDC Act § 505(j), that has not been withdrawn or suspended under FDC Act § 505(e)(1) through (5) of (j)(5), and that has not been withdrawn from sale for reasons of safety or effectiveness. A 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 the FDA as the "reference standard", in the Orange Book, must be used to conduct in vivo bioequivalence testing required for FDA approval.

As per FDA's Draft guidance for Industry, *"Draft Guidance for Industry, Referencing Approved Drug Products in ANDA Submission"* (Jan, 2017), An ANDA applicant must identify RLD and RS in its ANDA application as the basis of submission in Section 1.12.11.

The details of the reference listed drug product upon which our proposed generic drug product is based and details of Reference Standard Product are tabulated below.

*Hikma Pharmaceuticals USA Inc.* is applicant for the Reference product i.e. Dexamethasone tablets, 6 mg (Reference standard) (Application Number: A088316) along with being applicant for other strengths as shown in below table:

**Table 1: Reference Product Details**

| Information | Reference Listed Drug (RLD) Product | Reference Standard (RS) Product |
|---|---|---|
| Active Ingredient | DEXAMETHASONE | DEXAMETHASONE |
| Proprietary Name | DECADRON | DEXAMETHASONE |
| Dosage Form; Route | TABLET; ORAL | TABLET; ORAL |
| Strengths | 0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 4 mg and 6 mg | 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg and 6 mg |
| Reference Listed Drug | Yes | No |
| Reference Standard | No | 6 mg |
| TE Code | -- | BP |
| Application Number | N011664 | A084611 : 0.5 mg<br>A084613: 0.75 mg<br>A088306: 1 mg<br>A084610: 1.5 mg<br>A087916: 2 mg<br>A084612: 4 mg |

| Information | Reference Listed Drug (RLD) Product | Reference Standard (RS) Product |
|---|---|---|
| | | A088316: 6 mg |
| Approval Date | **0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg and 4 mg**: Approved Prior to Jan 1, 1982<br>**6 mg**: Jul 30, 1982 | July 25, 1975: 0.5 mg<br>June 03, 1975: 0.75 mg<br>September 15, 1983: 1 mg<br>May 19, 1975: 1.5 mg<br>August 26, 1982: 2 mg<br>July 19, 1978: 4 mg<br>September 15, 1983: 6 mg |
| Applicant Holder Full Name | MERCK AND CO INC | HIKMA PHARMACEUTICALS USA INC |
| Marketing Status | Discontinued *(**Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**)* | Prescription |

Among the strengths listed in above table, Dexamethasone Tablets, 1 mg and 2 mg held by Hikma is the only approved drug product strength in the 'active' section of Orange Book.

The **Orange Book pages** are appended as Annexure-1.

Additionally FDA has also recommended submitting the citizen petition for designation of RLD and selection of reference standard for dexamethasone tablets, 2 mg through Control correspondence (#13711 response dated September 3, 2020). Please refer below snaps for FDA's reference.

According to the Orange Book, there is no reference listed drug (RLD) or NDA for dexamethasone tablets USP, 2 mg. FDA Draft Guidance for Industry, *Referencing Approved Drug Products in ANDA Submissions* (January 2017) states that a drug product for which an ANDA is submitted must have, among other things, the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD. You propose dexamethasone tablets USP, 2 mg referring the RLD Decadron (N011664) as the basis of submission. We recommend that you submit a citizen petition under 21 CFR 10.25(a) and 10.30 requesting the designation of an RLD and selection of a reference standard for dexamethasone tablets USP, 2 mg drug product. However, a single ANDA for dexamethasone tablets USP 4 mg and 6 mg referencing NDA011664 may be submitted.

The lack of RLD and RS for Dexamethasone tablets, 1 mg and 2 mg prevents the filing of applications for generics equivalents. For this reason, the Petitioner respectfully requests FDA to designate *Hikma Pharmaceuticals USA Inc.*'s Dexamethasone Tablets, 1 mg and 2 mg as both a RLD and a RS. It is our understanding that Dexamethasone Tablets, 1 mg and 2 mg marketed under ANDA A088306 and A087916 respectively by Hikma Pharmaceuticals USA Inc., is the only currently available product in the U.S. market.

In a press release for the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial on 16 June 2020, Dexamethasone was recommended for use in COVID-19 patients with severe respiratory symptoms. Dexamethasone reduced deaths by approximately one third in patients requiring ventilation and by one fifth in those requiring oxygen.

WHO has also posted article in form of Question and Answers for Dexamethasone and its use in Covid-19.

On basis of above mentioned RECOVERY study, NIH (National Institute of Health) had published use of corticosteroid in Covid-19 treatment guideline. Therefore, we request to expedite the review of this Citizen Petition in order to protect and promote public health during the Covid-19 pandemic.

## III. ENVIROMENTAL 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 requested.

## V. CERTIFICATION

Petitioner certifies that, to the best of 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,**

11/30/2020

**Srinivas Gurram (Srini)**
Vice President & Head of RA and QA – North America
Zydus Pharmaceuticals (USA) Inc.

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