PHARMOBEDIENT

March 20, 2024

Division of Dockets Management
U.S. Food and Drug Administration
Department of Health and Human Services
Room 1061, l-IFA-305
5630 Fishers Lane
Rockville, MD 20852

ANDA Suitability Petition for Dantrolene Sodium Orally Disintegrating Tablets 25 mg, 50 mg and 100 mg

Dear Sir/Madam,

The undersigned submits this Suitability Petition pursuant to section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act ("FDC Act") and in accordance with 21 C.F.R. § 10.20, 10.30 and 314.93, to request that the Commissioner of the U.S. Food and Drug Administration ("FDA") declare that the drug product, Dantrolene Sodium Orally Disintegrating Tablets, 25 mg, 50 mg and 100 mg is suitable for submission in an Abbreviated New Drug Application ("ANDA").

A. Action Requested:

The Suitability Petition requests that the FDA determine and declare that Dantrolene Sodium Orally Disintegrating Tablets (ODT), 25 mg, 50 mg and 100 mg are suitable for submission in an Abbreviated New DrugApplication (ANDA). This Suitability Petition pursuant to Section 505(j)(2)(C) of the FDC Act and 21C.F.R. §314.93, is the appropriate mechanism for securing FDA authorization to submit an ANDA for a drug product that differs in dosage form from the Reference Listed Drug (RLD).

Dantrolene Sodium capsules are available in the market in 25 mg, 50 mg and 100 mg strength. The conventional capsules show poor patient compliance particularly by the geriatric patients who experience difficulty in swallowing, and by those who are bed ridden or who are traveling and donot have an easy access of water. To provide the patients with the most conventional mode of administration, there was a need to develop rapidly disintegrating dosage form, particularly one that disintegrates and dissolves/disperses in saliva and can be administered without need of water, anytime or anywhere.

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The Reference Listed Drug (RLD) upon which this petition is based is DANTRIUM (DANTROLENE SODIUM) CAPSUES from Par Sterile Products LLC which FDA approved prior to Jan 1, 1982 under NDA # 017443. DANTRIUM was marked in 25 mg, 50 mg and 100 mg strengths.

The relevant copy of the pages from the current Electronic Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) for DANTRIUM is provided as **Attachment 1.**

Approval of this Suitability Petition would allow the sponsor to submit Dantrolene Sodium Orally Disintegrating Tablets (ODT), 25 mg, 50 mg and 100 mg as an ANDA.

B. Statement of Grounds:

The FDC Act Section 505(j)(2)(C)(iii) and 21C.F.R. §314.93, provides for the submission of an Abbreviated New Drug Application for a drug product that has a different dosage form from the RLD product provided that the FDA has approved a suitability petition proposing such an application.

Dantrolene Sodium Capsules are indicated for:

- Controlling the manifestations of clinical spasticity resulting from upper motor neuron disorders in chronic spasticity
- Preoperatively to prevent or attenuate the development of signs of malignant hyperthermia

A copy of the most recent labeling for RLD under NDA # 17443 (Revised March 1, 2018) is provided as **Attachment 2**.

Pharmobedient proposes an alternative immediate-release orally disintegrating tablet dosage form, bioequivalent to Dantrium (Dantrolene Sodium Capsules), 100 mg, in the dosage strengths of 25 mg, 50 mg and 100 mg.

Table 1 presents the comparison between approved marketed and proposed drug product.

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Table 1 - Comparison of Approved Drug Products to Proposed Drug Product

Product Name	RLD Drug Products	Dantrolene Sodium Orally DisintegratingTablets by Pharmobedient Pharmaceuticals, LLC
Drug Substance	Dantrolene Sodium, USP	
Dosage Strengths	25 mg, 50 mg and 100 mg	25 mg, 50 mg and 100 mg
Dosage Form	Capsules	Orally disintegrating tablets
Route of Administration	Oral	
Indication	• Chronic Spasticity • Malignant Hyperthermia	
Method of administration (Dosing Information)	Dantrolene Sodium Capsules should be taken with water and swallowed whole.	Dantrolene Sodium Orally Disintegrating Tablets should be taken orally and should be sucked until completely disintegrated, and then swallowed.

Note: - *Formulation development of ODT tablet will be done to meet all the quality and regulatory requirements.*

The proposed labeling for Pharmobedient's Dantrolene Sodium Orally Disintegrating Tablets is provided as **Attachment 3;** with the changes annotated in track changes from the FDA approved labeling of the Immediate Release Capsules. The only differences between the two products' labeling are those related to the product description.

The orally disintegrating tablets formulation of Dantrolene Sodium will be developed by Pharmobedient to obtain an alternative immediate-release oral dosage form bioequivalent to RLD Dantrium (Dantrolene Sodium Capsules) by Par, that enhances and promotes therapeutic convenience, adherence and compliance:

- ODT do not require water or other liquids, so the developed product can be taken in situations where patients do not have access to water whatsoever contributing to treatment adherence.
- ODT serve as preferred dosage form for patients suffering from difficulty in swallowing, e.g. drug-induced esophagitis, elderly people or patients with impaired swallowing function.

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Considering the formulation release properties and the desired bioequivalence to the RLD formulation, the bioavailability of the 100 mg dosage strength of orally disintegrating tablets shall be studied against the 100 mg dosage strength of Dantrium (Dantrolene Sodium Capsules) 100 mg capsules as this is specified as the reference standard (RS) against which in vivo bioequivalence must be established. Thus, within the scope of the proposed ANDA approach, the drug product orally disintegrating tablets shall demonstrate bioequivalence (90% CI) against the RS in the two bioavailability studies (fasting and fed conditions) required by the Office of Generic Drug (OGD) Product-Specific Guidance for Generic Drug Development for bioequivalence studies of Dantrolene Sodium capsules, as provided in **Attachment 4**.

Therefore, the petitioner's request for the Commissioner to find that a change in dosage for (from capsule to ODT) in strengths of 25 mg, 50 mg and 100 mg (consistent with the approved RLD strengths) should raise no questions of safety or effectiveness, and the Agency should approve the petition.

C. Pediatric Waiver Request:

In September of 2007, Congress reauthorized the Pediatric Research Equity Act of 2003 (PREA) that amended the Federal Food, Drug, and Cosmetic Act to provide the Agency authority to require drug firms to study drugs in pediatric patients, if the Agency concludes that such study would provide beneficial health data for that patient population. The Act specifically requires that a request for a new dosage form is subject to a pediatric evaluation. The act also provides for a waiver from such requirement if the drug:

(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and

(II) is not likely to be used in a substantial number of pediatric patients.

The proposed product will contain the same labeling as RLD that permits dosing for all ages of pediatric patients for whom the drug is indicated. The gradual titration schedule is suggested based on the weight of pediatric patients. Since the proposed drug product contains the same dosage strengths as RLD, it is believed that it is not likely that this product would, nor should, post risk to pediatric patient on the safety and efficacy.

The petitioner hereby requests that a full waiver from the conduct of pediatric studies be granted for this petition to permit a subsequent ANDA filing.

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C. Environmental Impact
The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact
The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis, if requested by the Agency.

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 are unfavorable to the petition.

During the course of the review of this Suitability Petition, if there are any questions or comments, please do not hesitate to contact undersigned.

Sincerely,

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