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Via Regulations.Gov
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
SUITABILITY PETITION

Dear Sir/Madam:

The undersigned, on behalf of a client, 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. § 314.93 and 21 C.F.R. §§ 10.20 and 10.30, to request that the Commissioner of the U.S. Food and Drug Administration ("FDA") determine and declare that the drug products Acetaminophen Injection, 500 mg/50 mL (10 mg/mL) and 650 mg/65 mL (10 mg/mL), are suitable for submission in an Abbreviated New Drug Application ("ANDA").

A. Action Requested

The petitioner requests that the FDA declare that Acetaminophen Injection, 500 mg/50 mL (10 mg/mL) and 650 mg/65 mL (10 mg/mL), are suitable for submission in an ANDA. As designated in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"), the Reference Listed Drug ("RLD") upon which this petition is based is OFIRMEV® (acetaminophen) Injection, 1 g/100 mL (10 mg/mL), which is approved under NDA 022450, currently held by Mallinckrodt Hospital Products IP Ltd. The petitioner seeks to introduce new 500 mg/50 mL and 650 mg/65 mL strengths.

B. Statement of Grounds

Sections 505(j)(2)(A)(iii) and 505(j)(2)(C) of the FDC Act and 21 C.F.R. § 314.93 provide for the submission of an ANDA for a drug product that differs in ***strength*** from the RLD provided FDA has first approved a petition permitting the submission of such an application.

OFIRMEV (NDA 022450) contains 1000 mg of acetaminophen per 100 mL at a concentration of 10 mg/mL in an injectable solution dosage form. A copy of the current Orange Book entry for OFIRMEV is provided in ***Attachment 1***.

OFIRMEV is indicated for the management of mild to moderate pain in adult and pediatric patients 2 years and older; the management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older; and the reduction of fever in adult and pediatric patients. OFIRMEV is supplied in two presentations: a 100 mL glass vial and a 100 mL bag. A copy of the current RLD labeling is provided in ***Attachment 2***.

The proposed drug products contain the same active ingredient, acetaminophen, as the RLD, and therefore "are of the same pharmacological or therapeutic class as those of the [RLD]." 21 C.F.R. § 314.93(d)(1). The proposed drug products are also provided in the same injectable dosage form, with the same formulation, and at the same concentration (10 mg/mL) as the RLD, but in 500 mg/50 mL and 650 mg/65 mL strengths in a bag presentation. The petition is thus seeking a change in total drug volume and content from 1000 mg/100 mL to 500 mg/50 mL and 650 mg/65 mL.[1]

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[1] Although the ANDA would propose a change in the container closure presentation from the 100 mL vial to a 50 mL bag and 65 mL bag, respectively, the proposed changes to the container closure are not the subject of the Suitability Petition. *See* 21 C.F.R. § 314.93(b) (limiting suitability petitions to differences in route of administration, dosage form, strength, or active ingredient in combination product). Changes to container closure systems are among the permissible differences between an ANDA and RLD as long as clinical investigations are not necessary to establish the safety or effectiveness of the proposed drug product. FDA Guidance, *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019), at 4. Therefore, FDA does not need to address the safety or effectiveness of the proposed container closure presentations to resolve the Suitability Petition. Instead, any such questions would be resolved during FDA review of the ANDA.

The proposed drug products can nonetheless be expected to have the same therapeutic effect as the RLD when administered to patients for each condition of use in the RLD's labeling for which the applicant seeks approval. *See* 21 C.F.R. § 314.93(d)(2). This is because the proposed changes in strength are consistent with the dosing recommendations in the RLD label and fall within the approved dosages for the RLD. While the RLD label recommends a dose of 1000 mg when dosing every ***six*** hours for adults and adolescents weighing ≥ 50 kg, the label also recommends a 650 mg dose in this age group for dosing every ***four*** hours:

> **2.2 Recommended Dosage: Adults and Adolescents**
>
> Adults and adolescents weighing 50 kg and over: the recommended dosage of acetaminophen injection is 1000 mg every 6 hours or 650 mg every 4 hours, with a maximum single dose of acetaminophen injection of 1000 mg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 4000 mg per day (includes all routes of administration and all acetaminophen-containing products including combination products).
>
> Adults and adolescents weighing under 50 kg: the recommended dosage of acetaminophen injection is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of acetaminophen injection of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day (includes all routes of administration and all acetaminophen-containing products including combination products).

Table 1. Dosing for Adults and Adolescents

Age group	**Dose given every 4 hours**	**Dose given every 6 hours**	**Maximum single dose**	**Maximum total daily dose of acetaminophen (by all routes)**
Adults and adolescents (13 years and older) weighing ≥ 50 kg	650 mg	1000 mg	1000 mg	4000 mg in 24 hours

Adults and adolescents (13 years and older) weighing < 50 kg	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)

OFIRMEV Prescribing Information, § 2.2 (underlining added).

Further, as seen above, in adults and adolescents < 50 kg, the recommended dose ***may be lower than 650 mg*** because the RLD label instructs dosage to be determined based on patient weight. *Id.* To illustrate, for an adolescent weighing 40 kg, Table 1 of the RLD label recommends that a 500 mg dose be given every four hours (not to exceed the maximum total daily dose).

Similarly, the RLD label directs that the recommended dosages for children, neonates, and infants must also be determined by patient weight:

2.3 Recommended Dosage: Children

Children 2 to 12 years of age: the recommended dosage of acetaminophen injection is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of acetaminophen injection of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day.

Table 2. Dosing for Children

Age group	**Dose given every 4 hours**	**Dose given every 6 hours**	**Maximum single dose**	**Maximum total daily dose of acetaminophen (by all routes)**
Children 2 to 12 years of age	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)

2.4 Recommended Dosage For Treatment of Fever in Neonates and Infants

Neonates, including premature neonates born at ≥ 32 weeks gestational age, up to 28 days chronological age: the recommended dosage of acetaminophen injection is 12.5 mg/kg every 6 hours, to a maximum daily dose of acetaminophen of 50 mg/kg per day, with a minimum dosing interval of 6 hours.

Infants 29 days to 2 years of age: the recommended dosage of acetaminophen injection is 15 mg/kg every 6 hours, to a maximum daily dose of acetaminophen of 60 mg/kg per day, with a minimum dosing interval of 6 hours.

Table 3. Dosing for Treatment of Fever in Neonates and Infants

Age group	Dose given every 6 hours	Maximum total daily dose of acetaminophen (by all routes)
Neonates (birth to 28 days)	12.5 mg/kg	50 mg/kg
Infants (29 days to 2 years)	15 mg/kg	60 mg/kg

OFIRMEV Prescribing Information, §§ 2.3, 2.4. These pediatric dosing recommendations clearly contemplate doses far less than 1000 mg or 650 mg. To illustrate, according to Table 2, for a child weighing 20 kg who is dosed every six hours, the recommended dosage is 300 mg (not to exceed the maximum daily dose). For an infant weighing 10 kg, the recommend dosage is 150 mg every six hours (not to exceed the maximum daily dose), according to Table 3. Thus, the RLD's approved conditions of use include doses much lower than 1000 mg, encompassing both proposed strengths of 650 mg and 500 mg. As such, the proposed strengths are consistent with the RLD label and approved conditions of use.

Not only is the availability of lower strengths consistent with the dosing instructions of the RLD, it could aid clinicians in attaining the most effective dose, lead to less wasted drug product, lower costs, and reduce the risk of contamination of drug product. This is because, under the current RLD label, for doses less than 1000 mg, "the appropriate dose must be withdrawn from the container and placed into a separate container prior to administration" and "the unused portion must be discarded." OFIRMEV Prescribing Information, § 2.5. This is to "avoid the inadvertent delivery and administration of the total volume of the commercially available container." *Id.* And because the appropriate dose must be aliquoted aseptically from the vial to another sterile container and administered within 6 hours, *id.*, microbial or other contamination may also result from the additional product transfer step.

Although not at issue in the Suitability Petition, the proposed presentations would further help in this respect. The proposed container closure would be a PVC-free bag with one tube for the administration of infusion solutions. The availability of a 50 mL injection

bag and 65 mL injection bag would benefit clinicians and patients by increasing dispensing convenience and eliminating the risk of contamination from handling multiple containers.

For the reasons described above, the proposed new strengths do not raise questions of safety or efficacy for the proposed drug products. A 650 mg strength of the RLD administered every four hours was previously tested (alongside the 1000 mg strength administered every six hours) in a clinical study that demonstrated statistically significant analgesic efficacy of either dosing regimen of the RLD compared to placebo. *See* OFIRMEV Prescribing Information, § 14.1 (discussing Pain Study 2). In addition, single doses of the RLD at strengths of 500, 650, and 1000 mg were tested in pharmacokinetic ("PK") studies in adults, which demonstrated a dose-proportional PK profile of the RLD. *See id.* at § 12.3. Therefore, the Agency should conclude that clinical investigations are not necessary to demonstrate safety or effectiveness of the new strengths of the proposed drug products. There are no proposed changes in the ANDA labeling with the exception of changes describing the new strengths sought in this petition and the container closure presentations. Draft labeling for the proposed drug products is provided in ***Attachment 3***. Therefore, we request that FDA find that the changes in strength from 1000 mg/100 mL to 500 mg/50 mL and 650 mg/65 mL raise no questions of safety or effectiveness.

We request that FDA respond to this petition within the statutory 90-day deadline. *See* 21 U.S.C. § 355(j)(2)(C). The applicant believes, based on correspondence with providers, that there is an urgent need in the market for the lower strengths of this product due to waste of unused drug product when the currently-approved 100 mL container is aliquoted for lower doses.

The Pediatric Research Equity Act ("PREA"), enacted in December 2003, amended the FDC Act by requiring certain applications for a drug submitted under FDC Act § 505 to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is deferred or waived. *See* FDC Act § 505B(a)(I)(A)(i). Specifically, PREA applies to all applications for a new active ingredient, dosage form, indication, route of administration, or dosing regimen. *See id.* ANDAs submitted under an approved suitability petition for a change in strength are not subject to PREA requirements. *See* FDA, Draft Guidance for Industry, *How to Comply with the Pediatric Research Equity Act*, (Sep. 2005), at 4. Petitioner asserts that PREA is not applicable to the proposed Acetaminophen Injection, 500 mg/50 mL (10 mg/mL) and 650 mg/65 mL (10 mg/mL), drug products because the proposed changes concern only new strengths. As such, PREA should not serve as an impediment to the Agency granting this petition.

C. Environmental Impact

A claim for categorical exclusion of the requirements for an environmental assessment is made pursuant to 21 C.F.R. § 25.31.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), economic impact information will be submitted only when requested by the Commissioner following review of this petition.

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.

Sincerely,

Kurt R. Karst

Attachments:
1. FDA Orange Book page for OFIRMEV (acetaminophen) Injection
2. Prescribing Information for OFIRMEV (acetaminophen) Injection from DailyMed (updated April 2019)
3. Proposed Prescribing Information for Acetaminophen Injection, 500 mg/50 mL, 650 mg/65 mL