TECHREG SERVICES, INC.

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April 29, 2019

Division of Dockets Management
Food and Drug Administration
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 20852

SUITABILITY PETITION

The undersigned submits this petition under 21 CFR §10.20 and §10.30, as provided for in 21 CFR §314.93 and section 505(j)(2)(c) of the Federal Food, Drug and Cosmetic (FD&C) Act, to request the Commissioner of the Food and Drug Administration to provide a determination whether 8 mL and 16 mL fill volumes of Norepinephrine Bitartrate Injection, USP are suitable for inclusion in an Abbreviated New Drug Application (ANDA).

A. Action Requested

The undersigned requests that the Commissioner of the Food and Drug Administration determine whether the drug product Norepinephrine Bitartrate Injection, USP with fill volumes of 8 mL per vial and 16 mL per vial are suitable for submission in an ANDA. The reference listed drug (RLD) upon which this petition is based is LEVOPHED (norepinephrine bitartrate) injection, USP approved under NDA 007513 with a 4 mL per vial fill volume and a concentration of 1 mg/mL as norepinephrine free base. In addition to the already approved fill volume of 4 mL per vial, the petitioner seeks additional fill volumes of 8 mL per vial and 16 mL per vial, all with the same approved concentration of 1 mg/mL as norepinephrine free base.

B. Statement of Grounds

Section 505(j)(2)(A) of the FD&C Act permits the submission of an ANDA for a drug product that differs in strength from a listed drug after FDA has approved a petition submitted pursuant to Section 505(j)(2)(C) of the FD&C Act.

The ANDA criteria for sameness with the RLD cited in 21 CFR 314.94(a)(6) include route of administration, dosage form and strength, but do not explicitly include a statement regarding changes in fill volume of the compositionally identical bulk formulation as the RLD.

However, Section V.G.2 of the December 2016 FDA *Guidance for Industry - ANDA Submissions – Refuse-to-Receive Standards* states: “FDA will RTR [Refuse to Receive] an ANDA whose subject is a parenteral drug product if its fill volume deviates from the RLD drug product and the deviation is not permitted. ANDA parenteral (injectable) drug products should contain the same concentration and total drug content per container as the RLD. Therefore, a deviation from the fill volume (total drug content) of the RLD parenteral drug product may constitute a change in strength. A change in strength must

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first be approved via the suitability petition process (see section III.F of this guidance) before it can be proposed in an ANDA submission."

Similarly, footnote 14 of the June 2015 FDA *Guidance for Industry - Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* states: "An ANDA that references a currently approved reference listed drug (RLD) is generally expected to have the same labeled vial fill size as the RLD. In the event of a suitability petition permitting a change in vial fill size, the basic principles of this guidance would be applied to the petitioned ANDA."

In effect, for the purpose of assessing sameness of the generic drug to the RLD, the Agency has defined the strength of the drug to consist of two components, concentration and fill volume, and a change in either or both constitutes a change in strength. Accordingly, the suitability petition is the appropriate mechanism for addressing this proposal.

This proposal is further justified based on the following:

- Since the individual drug product vials are combined with additional dilution in 250-1000 mL of 5% Dextrose solution for intravenous administration, approval of this petition would provide higher vial fill volumes for further dilution, hence minimizing the number of vials of drug product needed to achieve the appropriate dilution and mitigating the potential for contamination related to handling.
- A comparison of the RLD to the proposed drug product is provided in Table 1. All listed criteria for the proposed drug product will be the same as for the RLD with the addition of the 8 mL/vial and 16 mL/vial fill volumes. There will be no changes in the proposed labeling aside from the corresponding additional fill volumes in the How Supplied section. The uses, indications, warnings, and directions for use will remain the same as those for the previously approved drug product.
- The 4 mL/vial, 8 mL/vial and 16 mL/vial fill volumes for the proposed drug product are readily differentiated from each other since the vial sizes will also be correspondingly larger and the immediate container and all other labeling will clearly state the fill volume.

There is no information known to the petitioner which is unfavorable to the petitioner's position.

C. Environmental Impact

A categorical exclusion is claimed under 21 CFR §25.31(a) since the proposed action does not increase the use of the active moiety relative to the continued use of a 4 mL fill only.

D. Economic Impact

Pursuant to 21 CFR §10.30(b), an economic impact analysis will be provided upon request.

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.

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Table 1. Comparison of the Reference Listed Drug and Proposed Drug Product

Criteria	Reference Listed Drug	Proposed Drug Product
Name	LEVOPHED (norepinephrine bitartrate) injection, USP	Norepinephrine bitartrate injection, USP
Indications and Usage	As per current LEVOPHED labeling	As per current LEVOPHED labeling
Active Ingredient	Norepinephrine bitartrate	Norepinephrine bitartrate
Strength (Concentration)	1 mg/mL as norepinephrine free base	1 mg/mL as norepinephrine free base
Fill Volume(s)	4 mL/vial	4 mL/vial, 8 mL/vial, 16 mL/vial
Dosage Form	Injectable	Injectable
Route of Administration	Intravenous	Intravenous