February 2, 2022

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

SUITABILITY PETITION

Dear Sir/Madam,

The undersigned petitioner submits this petition pursuant to section 505(j)(2)(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act, in accordance with the 21 CFR § 10.20 and § 10.30, to request the Commissioner of the Food and Drug Administration (FDA) to declare that the proposed drug product Diazepam Injection USP, 20 mg/4 mL (5 mg/mL) single dose prefilled syringe is suitable for consideration in an Abbreviated New Drug Application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that, Diazepam Injection USP, 20 mg/4 mL (5 mg/mL) single dose prefilled syringe is suitable for submission as an ANDA. The Reference Listed Drug product (RLD), upon which this petition is based, is VALIUM (diazepm) Injection, 5 mg/mL, New Drug Application ("NDA") N016087 currently held by HOFFMANN LA ROCHE INC., as designated in the current Electronic Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (i.e., Orange Book) (refer Attachment 1). The RLD is in discontinued state in the Orange Book (*Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons*). All

other approved generics are currently marketed in 10 mg/2 mL (5 mg/mL) single dose prefilled syringe and 50 mg/10 mL (5 mg/mL) multiple dose vial.

The petitioner hereby seeks a change in fill volume from 10 mg/2 mL (5 mg/mL) single dose prefilled syringe to 20 mg/4 mL (5 mg/mL) single dose prefilled syringe. It should be noted that the change in fill volume does not constitute a change in concentration.

B. Statement of Grounds

Section 505(j)(2)(C) of the FD&C Act provides for the submission of an ANDA for a drug product that differs in strength (or in case of parenteral products, total drug content) from the RLD provided that the FDA has approved a petition that proposes filing such an application. The FDA's informal policy requires submission of a suitability petition to obtain authorization of an ANDA for a parenteral drug for a drug container size (or volume) in which the total content of the container is different from the total content of container approved for the listed drug[1]. Additionally, a parenteral product is suitable for an ANDA if the formulation of the generic product is identical to the RLD with the exception of antioxidants, buffers and/or preservatives, per 21 CFR 314.96(a)(9)(iii). The RLD VALIUM is under discontinued status in the current Orange Book – *Approved Drug Products with Therapeutic Equivalence Evaluations* and the discontinuation reason mentioned by the Federal Register is that product was not discontinued or withdrawn for safety or efficacy reasons. Further, the Prescribing Information (PI) of this RLD is not available for reference in the public domain because this product has been discontinued.

[1] FDA has an informal policy of requiring the submission of a suitability petition to obtain authorization for an ANDA for a parenteral drug in a drug-container size (or volume) in which the total content of the container is different from the total content of a container approved for the listed drug or in a previous suitability petition for an ANDA. This policy applies notwithstanding that there is no change in the concentration of the parenteral drug. FDA's informal policy of requiring a suitability petition for a different parenteral drug container size as a different "strength" under 21 U.S.C. § 355(j)(2)(C) cannot be justified as a general rule, because container size and strength do not correlate with each other in all cases. FDA is required to approve ANDAs meeting the standards of § 355(j)(2)(A). A parenteral drug that differs from the listed drug only in the size or total contents of its container does not have a different strength, and therefore it meets the requirement of § 355(j)(2)(A)(iii).

Hence, the Reference Standard (RS) Diazepam Injection USP, 10 mg/2 mL (5 mg/mL) single dose prefilled syringe, Abbreviated New Drug Application ("ANDA") A210363 currently held by BELOTECA INC is used as reference to develop the proposed drug product. A comparison of the approved ANDA for Diazepam Injection USP, 10 mg/2 mL fill volume to the proposed Diazepam Injection USP, 20 mg/4 mL fill volume is provided in Table 1A & 1B below:

Table 1A. Comparison of Approved Product with Petitioner's Proposed Product

Product Details	**Approved Product Diazepam Injection USP ANDA # A210363**	**Petitioner's Proposed Product Diazepam Injection USP**
Active Ingredient	Diazepam	Diazepam
Route of Administration	Injection	Injection
Dosage Form	Injectable	Injectable
Volume (per container)	2 mL	4 mL
Strength (per mL)	5 mg	5 mg
Strength (per container)	10 mg	20 mg
Package Type	Single Dose Prefilled Syringe	Single Dose Prefilled Syringe

Table 1B. Comparison of Formulations

Drug Product Components	**Function**	**Approved Product Diazepam Injection USP ANDA # A210363**	**Petitioner's Proposed Product Diazepam Injection USP***				
		Per mL	**mg/mL**		**% w/v**		**% v/v**
Diazepam	Active Pharmaceutical Ingredient	5 mg	5		0.5		NA
Propylene Glycol	Solubilizer	40%	414.4		41.44		40 [a]
Alcohol	Solubilizer	10%	81		8.1		10 [b]
Sodium Benzoate	Buffer	5%	49	50	4.9	5.0	NA
Benzoic Acid	Buffer		1		0.1		NA
Benzyl Alcohol	Preservative	1.5%	15		1.5		1.5 [c]
Water for Injection	Vehicle	q.s. to 1 mL	q.s. to 1 mL		q.s. to 100		

*The quantity is mentioned on the basis of approved Q1/Q2 Controlled Correspondence for 2 mL fill.
a – Density of Propylene Glycol is 1.036 g/mL
b – Density of Alcohol is 0.81 g/mL
c – Density of Benzyl Alcohol is 1.0 g/mL
NA – Not Applicable

The proposed product is identical in indication, active ingredient and route of administration to the approved drug products, RLD – VALIUM (diazepam) Injection, 5 mg/mL and RS – Diazepam Injection USP, 10 mg/2 mL (5 mg/mL) single dose prefilled syringe. The petitioner has done extensive market research about drug product usage in older children and adults patient population as well as prescribing information of the approved drug products, also indicates the dose up to 20 mg.

The proposed change in fill volume is clearly provided for in the approved labelling for RS. Changes in the labelling would be limited to describing the proposed new presentations. The product's usage, indications, warnings and precautions will remain the same as that of the RS.

As per the prescribing information RS – Diazepam Injection USP, 10 mg/2 mL (5 mg/mL), (For full details Refer RS – Diazepam Injection USP, 10 mg/2 mL (5 mg/mL) PI in Attachment 2).

> **DOSAGE AND ADMINISTRATION**
>
> The usual recommended dose in older children and adults ranges from 2 mg to 20 mg intramuscular or intravenous, depending on the indication and its severity.
>
> **Endoscopic Procedures:**
>
> Usual Adult Dosage
>
> Titrate intravenous dosage to desired sedative response, such as slurring of speech, with slow administration immediately prior to the procedure. Generally, 10 mg or less is adequate, but up to 20 mg intravenous may be given, particularly when concomitant narcotics are omitted.

As noted in the prescribing information, dosing up to 20 mg is recommended in older children and adults. Therefore, the petitioner proposes to develop the product as a single dose with a 4 mL fill volume for patients that require 20 mg dose. Currently only 2 mL fill as single dose prefilled syringe and 10 mL fill multiple-dose vials are available in the market.

In addition to being supported by prescribing information, the use of 20 mg intravenous doses of diazepam is supported in clinical practice guidelines and well documented in clinical literature. A primary use of these doses is for the indication of acute alcohol withdrawal. The American Society of Addiction Medicine guideline on Alcohol Withdrawal Management[2] and the World Federation of Societies of Biological Psychiatry guidelines for treatment of substance use and related disorder related to alcoholism[3] recommends benzodiazepines, including diazepam, as first-line agents for managing most forms of alcohol withdrawal. 20 mg doses of diazepam are specifically recommended as front loading doses to achieve rapid control of withdrawal symptoms in both of these guidelines.[2,3] Gold et al. concluded that escalating boluses of diazepam (including 20 mg doses) reduced the need for mechanical ventilation in patients treated for severe alcohol withdrawal.[4] A review publication on the use of diazepam for the treatment of moderate to severe alcohol withdrawal cites many additional publications and describes the rapid and safe use of diazepam compared to other benzodiazepines due to its pharmacokinetic properties.[5] This publication also refers to doses of 20 mg.[5] A single dose prefilled syringe containing a 20 mg dose of diazepam will allow for convenient and safe administration of this dose in the indicated clinical conditions.

The petitioner proposes to file an ANDA with 4 mL fill single dose prefilled syringe with approved composition and dosage form identical to the approved ANDA (identical Q1/Q2 with respect to the composition). The details of the proposed 4 mL fill volume and approved 2 mL fill volume product (ANDA # A210363) are provided in Table 1B.

[2] The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management, Journal of Addiction Medicine: May/June 2020 - Volume 14 - Issue 3S - p 1-72

[3] Michael Soyka, Henry R. Kranzler, Victor Hesselbrock, Siegfried Kasper, Jochen Mutschler, Hans-Jürgen Möller & The WFSBP Task Force on Treatment Guidelines for Substance Use Disorders (2017) Guidelines for biological treatment of substance use and related disorders, part 1: Alcoholism, first revision, The World Journal of Biological Psychiatry, 18:2, 86-119.

[4] Gold JA, Rimal B, Nolan A, Nelson LS. A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. Crit Care Med. 2007 Mar;35(3):724-30.

[5] Weintraub, S.J. Diazepam in the Treatment of Moderate to Severe Alcohol Withdrawal. CNS Drugs 31, 87–95 (2017).

The availability of the proposed fill with single dose presentation may provide several benefits as noted below:

1. It provides for a ready to administer dosage form in a prefilled syringe that does not require preparation prior to administration which results in time savings and possibly decreases the possibility of contamination and errors that can occur during dose preparation.
2. It allows potential for safer use of the product as there is a reduced possibility of the container being treated as a multiple use container over a longer period of time.
3. It may permit easier stocking as the storage space is limited in most hospital pharmacies and areas where diazepam is stored and used.

The FDA has a long history and precedents for approving ANDA suitability petitions related to the changing in the package sizes based upon need in medical practice. The request made by the petitioner for the submission of the ANDA for Diazepam Injection, 4 mL single dose prefilled syringe is no different than the requests that have been previously approved by the FDA. Some of the past FDA approvals are included to serve as an example herein. The examples of such suitability petition are:

- Docket Number: FDA-2009-P-0068-0001/CP for Potassium Acetate Injection, USP 200 mEq (2 mEq/mL, 100 mL fill) in a 100-cc plastic, pharmacy bulk plastic;
- Docket Number FDA-2010-P-0114 for Pyridoxine Hydrochloride Injection USP, 100 mg/mL, 30 mL multi-dose vials from Abraxis;
- Docket Number: FDA- 2012-P-0387 for Fludeoxyglucose F-18 Injection, 1-20 mCi/rnL at End of Synthesis (EOS);
- Docket Number: FDA-2009-P-007 - change in strength (total drug content) from that of the listed drug;
- Docket Number: FDA-2006-P-0210 (Legacy Docket No. 2006P-0095): Piperacillin and Tazobactam for Injection, 13.5 g/vial, Pharmacy Bulk Package (containing piperacillin sodium equivalent to 12 g of piperacillin and tazobactam sodium equivalent to 1.5 g of tazobactam)

As described above, there are no proposed changes in the labeling with the exception of the obvious changes in strength (total content by virtue of volume). The proposed change in fill

volumes represents dosage fill volumes that are consistent with the dosing recommendations of the Listed Drug (LD)'s approved labeling. The uses, indications, warnings and directions for use will remain the same as that of the LD. Draft labeling for the proposed product is included in Attachment 3, and the LD's approved labeling is provided in Attachment 2.

Therefore, the petitioner's request for the commissioner is to find that a change in strength (total drug content from 10 mg Diazepam in 2 mL single dose prefilled syringe package to 40 mg Diazepam in 4 mL single dose prefilled syringe package) should raise no concerns about the safety or effectiveness of the proposed product as compared to the Approved drug and the Agency should approve the petition. Furthermore, this request is in-line with the requests previously approved by the Agency for changes in strength (fill volume) and can further provide benefits inclusive of providing a package size that is well desired by the healthcare community which will likely provide, significant cost savings, use convenience and most importantly safe use of Diazepam Injection.

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.

D. Economic Impact

Pursuant to 21 CFR § 10.30(b), upon request by the Commissioner, the petitioner will, submit an economic impact information.

E. Certification

The undersigned certifies that to the best of its knowledge, 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.

We respectfully request the Agency to approve our ANDA Suitability Petition.

Sincerely,

Michelle R. Ryder

Digitally signed by Michelle R. Ryder
Date: 2022.02.02 15:26:05 -07'00'

Michelle Ryder
Executive Director
Lachman Consulting Services, Inc.