Request for a Waiver

COVID-19 Vaccine
BNT162
(PF-07302048)

Request for Exception
to the
21 CFR 610.15(a)
Requirement for a Preservative

JULY 2021

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INTRODUCTION

This submission is a request for an exception to the regulatory requirement under 21 CFR 610.15(a) that a vaccine product in a multi-dose container should contain a preservative. As discussed more fully below, the requested exception is necessary due to exigent circumstances resulting from the COVID-19 emergency that would otherwise delay production of large quantities of the vaccine necessary for global distribution. The exception is further justified by the favorable post-authorization experience following distribution of more than 871,000,000 doses of vaccine in this multi-dose, non-preserved presentation under the US Emergency Use Authorization (EUA 27034) and other global authorizations from the receipt of the first temporary authorization for emergency supply in the UK on 01 December 2020 through 30 June 2021.

Pfizer and BioNTech have developed a vaccine intended to prevent coronavirus disease 2019 (COVID-19), which is caused by the virus SARS-CoV-2. The vaccine, as authorized under EUA 27034, is a concentrated liquid formulation stored frozen at -90 to -60 °C in a 2 mL Type 1 glass vial, with provisions for short-term storage for up to two weeks at -20 ±5 °C and up to 1 month at 2-8 °C until administration, as described in Module 3.2 of the BLA. Due to the urgency of the COVID-19 pandemic and the immediate and ongoing need to manufacture large numbers of doses for global use throughout 2021 and 2022, a multi-dose, preservative-free vial presentation remains an important tool to enable sufficient global supply, even while a single-dose vial is also under development. Therefore, Pfizer and BioNTech intend to commercialize the current frozen liquid formulation filled into a multidose vial. After dilution with normal saline, six doses would be withdrawn from the multidose vial. The dosage and administration section on the label will include detailed instructions for the health care provider to perform the dilution with 0.9% Sodium Chloride Injection, USP.

Pfizer and BioNTech acknowledge that 21 CFR 610.15(a) requires that

> *Products in multiple-dose containers shall contain a preservative,…*

However, 21 CFR 610.15(d) states that

> *The Director…may approve an exception or alternative to any requirement in this section. Requests for such exceptions or alternatives must be in writing.*

Pfizer and BioNTech are hereby making a written request for an exception to 21 CFR 610.15(a) for the BNT162b2 vaccine as a multi-dose preservative-free presentation.

The justification for this exception request is provided herein including details regarding Pfizer and BioNTech's plans for ensuring that the vaccine will meet the statutory and regulatory requirements for identity, safety, purity, and potency. Please note, this exception has been requested and authorized under Emergency Use Authorization 27034 and is requested to remain in place upon BLA approval.

1. BACKGROUND

1.1. Proposed Multi-dose Vial Design and Proposed User Instructions

The BNT162b2 drug product is frozen at -90 to -60 °C for storage and distribution with provisions for short-term storage for up to two weeks at -20 ±5 °C and up to 1 month at 2-8 °C until administration, as described in Module 3.2 of the BLA. The drug product is provided as a concentrate that is diluted at point of use prior to administration.

On the day of administration, the thawed vaccine vial is prepared for use. 0.9% Sodium Chloride Injection, USP (Normal Saline) is added to the vial to increase the volume of the vaccine solution for dosing to ensure that the injection volumes are appropriate for administration. The vial is labeled with the time of Normal Saline dilution and must be discarded within 6 hours after initial dilution. Dose administration of the BNT162b2 vaccine involves withdrawal of the prescribed dose from the vial into a delivery system such as a syringe.

The dilution scheme for vaccine dosed under the EUA is representative of the proposed dose administration instructions for planned commercial supply under an approved BLA.

1.2. Justification for the Unpreserved Multidose Vial

The BNT162b2 drug product is filled into 2 mL vials at a concentration of 0.5 mg/mL RNA contained in lipid nanoparticles (LNPs). Formulation development studies conducted to date do not support long-term storage of formulations at lower RNA or LNP concentrations without a change to the formulation. A new formulation to enable lower strengths of RNA LNP will require additional time to gain global regulatory authorization and build additional production capacity to supply global demand.

In addition to the formulation limitations, the drug product manufacturing sites have limitations on the lowest volume that can be filled into the vial in a reliable and consistent manner. This has been determined to be 0.3 mL for many of the drug product manufacturing lines that have been qualified for this vaccine drug product. Due to these constraints, the final filled vial will contain enough concentrated active vaccine to supply 6 doses. Normal Saline must be added to the vial in order to achieve an adequate injection volume regardless of whether the vial is used as a single dose or a multi dose vial. If used as a single dose vial, 5 additional doses would be discarded after removal of a single dose. The use of this product as a multi dose vial therefore provides 6 times more doses than if used as a single dose vial and prevents wastage of a critically needed vaccine.

Pfizer and BioNTech have assessed the risks of this approach by taking into consideration formulation factors including, but not limited to, pH, solvent system, osmolality, drug product storage temperature, and solution properties, which may impact the ability of the finished drug product to support or inhibit microbial growth. Additionally, prior knowledge from extensive experience with other products and data from platform formulations and commonly used infusion fluid studies have been used to evaluate dilution and administration risks.

Pfizer performed the microbial challenge assessments based on Dr. Metcalfe's paper[1] which included the panel of microbes in USP <51> and used prepared vaccine dosing solutions. In the study, samples were spiked with a low level inoculum (<100 cfu/mL) of *S.aureus, E. coli, Ps. aeruginosa, A. niger* (name changed to *A. brasiliensis*), and *C. albicans*, held at 20-25 °C, and then assessed for growth at time points up to 16 hours. Testing revealed no significant growth for any of the organisms within 12 hours of inoculation with storage at 20-25 °C which is defined as not more than 0.5 $\log_{10}$ unit higher than the previous value measured cfu. The results of this study are provided in Section 3.2.P.2.6 Compatibility and provide assurance for the microbial integrity of the product over 6 hours. The in-use period of 6 hours is necessary to ensure adequate time is provided to prepare and administer 6 doses and is in alignment with WHO policy on the use of opened multi-dose vaccine vials[2].

The exception is further justified by the favorable post-authorization experience following distribution of more than 871,000,000 doses of vaccine in this multi-dose, non-preserved presentation under the US Emergency Use Authorization (EUA 27034) and other global authorizations from the receipt of the first temporary authorization for emergency supply in the UK on 01 December 2020 through 30 June 2021.

As noted in 21 CFR 610.15, "Any preservative used … shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature." Given the lipidic nature of the lipid nanoparticles, compatibility with common preservatives is not expected. As the microbial growth assessment study results support an in-use period of up to 6 hours, the exclusion of a preservative which may otherwise compromise potency is prudent.

2. SUMMARY: REQUEST FOR EXCEPTION

Pfizer and BioNTech hereby request an exception from 21 CFR 610.15(a) regarding the requirement for using a preservative in a Multi-Dose Vial for commercial supply of the candidate vaccine under BLA 125742.

REFERENCES

1 Metcalfe JW. Microbiological quality of drug products after penetration of the container system for dose preparation prior to patient administration. American Pharmaceutical Review 2009;(Jan/Feb):84-9.

2 WHO Policy Statement: Multi-Dose Vial Policy (MDVP) – Handling of Multi-Dose Vaccine Vials After Opening, Revision 2014. WHO/IVB/14.07. Available at https://apps.who.int/iris/bitstream/handle/10665/135972/WHO_IVB_14.07_eng.pdf