

**Considerations in Pfizer-BioNTech COVID-19 vaccine preparation in clinic: Quality vs quantity**

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Vaccination is one of the key components of defeating a pandemic. Three coronavirus disease 2019 (COVID-19) vaccines have received Food and Drug Administration (FDA) emergency use authorization (EUA), with more to come in the near future. One of those products, the Pfizer-BioNTech COVID-19 vaccine, was approved by FDA in August 2021 for use in individuals 16 years of age or older and continues to be available via EUA for individuals 12 through 15 years of age and for the administration of a third vaccine dose in certain immunocompromised individuals.

The Moderna and Janssen COVID-19 vaccines come ready to be administered. Pfizer-BioNTech COVID-19 vaccine administration is uniquely different from administration of other COVID-19 vaccines in terms of preparation, because it requires an additional step of dilution. The undiluted Pfizer-BioNTech vaccine must be diluted with 1.8 mL of preservative-free (PF) 0.9% sodium chloride injection, commonly known as normal saline (NS), before administration.

The dilution process is considered simple, but inconsistency in certain steps of the process can cause variation in dosing. While preparing the vaccine vials for dilution, some of the steps can be easily overlooked because they are not clearly stated in the manufacturer's guideline<sup>1</sup> on vaccine dilution. Therefore, it is necessary to share these considerations with other pharmacists, clinicians, and/or vaccinators to achieve consistency in preparation.

**NS withdrawal.** In the cleanroom environment, adding to the vial a volume of air equal to the volume of the drug intended to be withdrawn is a typical step of the aseptic technique. The manufacturer's guideline does not include this step. If Pfizer-BioNTech COVID-19 vaccine dilution is performed in an International Organization for Standardization (ISO) class 5 environment, this step can be adopted. Compared to ISO class 5 room air, the human body carries the highest bioburden. Therefore, the aseptic technique is still an important factor in not contaminating any critical part of the syringe preparation operation.

When utilizing the aseptic technique, the introduction of bioburden into the sterile saline vial or vaccine vial will be significantly limited. The highest chance of bioburden intrusion might occur when the needle punctures the vial and the undiluted vaccine is removed. If the dilution is performed in room air that is unclassified and uncontrolled, adding uncontrolled air of equal volume into the vial may increase the likelihood of introducing contamination at the beginning of the preparation process.

Additionally, without adding air to the PF NS vial, direct removal of 1.8 mL of NS from a vial containing 2 mL of NS will generate negative pressure inside the vial. Of note, the 2-mL PF NS product from Fresenius Kabi comes in a 3-mL single-dose vial. Therefore, removing 1.8 mL of NS means removing 60% of the 3-mL container volume, which results in pressure buildup inside the vial. Under negative pressure, it is challenging to keep the syringe plunger at the 1.8 mL mark when the needle is removed from the NS vial. Clinicians should consider holding the plunger in the same position while removing the needle from the NS vial, or withdrawing more than 1.8 mL of NS diluent and then adjusting the syringe volume by ejecting the extra NS from the syringe after removing the needle from the vial.

**Addition of 1.8 mL of PF NS diluent to the vaccine vial.** When 1.8 mL of PF NS diluent is pushed into the undiluted vaccine vial, it will create positive pressure inside the vaccine vial since the size of the vaccine vial is similar to that of a typical 2-mL NS vial. This positive pressure will push the solution back into the syringe if not enough force is applied to the plunger. Clinicians should consider constantly applying enough pressure to push the NS diluent into the vaccine vial against the positive pressure. Do not let the plunger retract back or oscillate while adding NS diluent into the vial. When the plunger is retracted, air from the vial can be introduced into the syringe; then the air bubbles in the syringe barrel will expel the NS diluent in the needle hub into the vaccine vial when the vial injection is completed.

As indicated in the manufacturer's guideline for neutralizing the pressure of the vial, it is important to draw about 2.1 mL of air from the diluted vaccine vial into the syringe barrel by releasing the plunger after 1.8 mL of NS is completely delivered into the vaccine vial. The positive pressure inside of the vial will push the plunger back close to the 1.8 mL mark. At this time, the remaining NS diluent left in the needle hub will be retrieved into the syringe barrel. This visible amount of NS solution confirms that the NS diluent in the needle hub has not been accidentally added into the vaccine vial and, therefore, has not affected the total desired injected volume of 1.8 mL of diluent. If, on the other hand, the additional NS diluent from the needle hub is added to the syringe as a result of flushing the syringe or letting the plunger oscillate while adding NS into the vaccine vial or retrieving the plunger, the concentration of the final vaccine solution will be lower than desired due to the additional NS volume from the needle hub.

According to a study performed by syringe manufacturer Becton Dickinson, a 3-mL syringe (barrel and needle hub combined) can have a dead space of as much as 0.15 mL.

When 0.15 mL is added into the target transfer volume of 1.8 mL, that results in a less than 10% increase in volume and the concentration of the vaccine will not be lower than 90%. Therefore, this margin of deviation is allowed, especially when the Centers for Disease Control and Prevention is allowing the COVID-19 vaccines to be given even when a dose of 50% of the recommended vaccine volume can be considered as a full dose. However, avoidance of the additional NS diluent can be a good pharmaceutical practice to prepare consistent doses even though the lower final vaccine concentration may fall into the clinically acceptable dosing level, marginally.

**Preparation of a 0.3-mL vaccine dose.** With proper calculation and considering the dead space of the needle hub, the final volume of Pfizer-BioNTech vaccine after dilution is not enough for 7 doses. Since the dead space volume inside of the needle hub can be easily overlooked, it is possible to miscalculate that there can be 7 doses in a vaccine vial. Before dilution, the vaccine vial contains 0.45 mL of vaccine. Adding 1.8 mL of NS diluent will provide a total volume of diluted vaccine of 2.25 mL. If this volume is divided by 0.3 mL, it will give 7 doses by calculation. However, this calculation does not account for the volume loss due to the dead space in the needle hub. This volume will remain in the needle hub after delivering 0.3 mL of vaccine. The volume loss from the dead space has been well summarized in the literature across organizations.<sup>2</sup> For example, even when a low dead volume (LDV) syringe is used, the volume from the needle hub is 0.035 mL or less,<sup>2</sup> which will be added into 0.3 mL of injecting volume. Therefore, each dose will need to be about 0.335 mL in order to provide 0.3 mL into the patient's arm. The theoretical total volume of a diluted vaccine vial is shown in Box 1, and the possible numbers of syringes per vaccine vial are calculated in Table 1. As shown in Table 1, there is not enough volume for the seventh

dose even with use of an LDV syringe and needle, theoretically. Additionally, big air bubbles were often found in some syringes during inspections of 7-dose batches in a clinic setting.

To achieve herd immunity against COVID-19 effectively in a timely manner, it is important not only to maximize the numbers of doses from the vaccine vials but also to prepare quality doses consistently. Considering the unique preparation steps for the Pfizer-BioNTech COVID-19 vaccine, the following critical points can help to prepare proper 0.3-mL vaccine doses consistently:

- During NS withdrawal, consider the effects of negative pressure.
- Dilution of 1.8 mL NS to the vaccine vial, consider the effects of positive pressure while injecting diluent and removing air.
- During syringe preparation of the 0.3-mL vaccine dose, consider dead space in the needle hub and perform a quality control check on a 7-dose batch.

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**Box 1.** Theoretical Total Volume in Diluted Vial of Pfizer-BioNTech COVID-19 Vaccine

Vaccine volume per vial	0.45 mL
Volume of diluent (normal saline)	1.8 mL
Final vaccine volume per vial after dilution	2.25 mL

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**Table 1.** Possible Numbers of Prepared Syringes per Pfizer-BioNTech COVID-19 Vaccine Vial

	<b>Ordinary Syringe/Needle</b>	<b>LDV Syringe/Needle</b>
Vaccine dose, mL	0.3	0.3
Dead volume, mL	0.07 <sup>3</sup>	0.035 <sup>2</sup>
Volume needed per syringe, mL	0.37	0.335
No. of prepared syringes per vaccine vial	$2.25^a/0.37 = 6.08$	$2.25 \text{ mL}^a/0.335 \text{ mL} = 6.72$

Abbreviation: LDV, low dead volume.

<sup>a</sup>Each vial of Pfizer-BioNTech COVID-19 vaccine contains 2.25 mL of vaccine.

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