



FDA Guidance on “Temporary Policy on Repackaging or Combining Propofol Drug Products During the COVID-19 Public Health Emergency”: Drug Product Quality Consideration

**SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval
Day 1, Session 1: COVID-19 Impact**

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Learning Objectives

- Recognize the purpose of the guidance
- Review the propofol injectable emulsion drug products and their physicochemical and stability properties
- Discuss the repackaging or combining propofol injectable emulsion drug products based on the compatibility

Temporary Policy on Repackaging or Combining Propofol Drug Products During the COVID-19 Public Health Emergency



- Published April 2020
- Location
 - <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/temporary-policy-repackaging-or-combining-propofol-drug-products-during-covid-19-public-health>
- Issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency.

Why this Guidance is Needed



- Propofol is on the Drug Shortages List
- Hospitals have had difficulty obtaining adequate supplies to care for critically ill COVID-19 patients
- Healthcare professionals requested guidance on repackaging or combining 20 mL or smaller FDA-approved Propofol Injectable Emulsion drug products into larger vials (e.g. to 50 mL to 100 mL sterile containers secondary to supply short falls of 50 mL and 100 mL Propofol Injectable Emulsion)

Why this Guidance is Needed (cont.)



- FDA-approved labeling states that “propofol undergoes oxidative degradation in the presence of oxygen and is therefore packaged under nitrogen to eliminate this degradation path.”
 - Exposing propofol to oxygen during repackaging would be in conflict with the approved labeling and would fall outside of the policy in the [Repackaging Guidance](#).
- Pharmacies asked about “combining” the contents of different manufacturers’ propofol products and placing them in the same container.
- Propofol is not covered by other temporary policies for compounding of certain drugs for hospitalized patients during the COVID-19 public health emergency, because of quality concerns.

Purpose of the Guidance



- Provides a temporary policy regarding the repackaging or combining of propofol by state-licensed pharmacies (including hospital pharmacies), federal facilities, and outsourcing facilities for use in hospitals that are having difficulty obtaining adequate supplies.
- Addresses certain practices that fall outside of FDA's guidance on *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing* (the [Repackaging](#) guidance).
- Valid during the period of the COVID-19 public health emergency or until withdrawn by FDA as no longer appropriate.

FDA Approved Labeling for Propofol Drug Products

INDICATIONS and USAGE



- Propofol injectable emulsion is an IV general anesthetic and sedation drug that can be used as described in the table below.

Indication	Approved Patient Population
Initiation and maintenance of Monitored Anesthesia Care (MAC) sedation	Adults only
Combined sedation and regional anesthesia	Adults only (see PRECAUTIONS)
Induction of General Anesthesia	Patients greater than or equal to 3 years of age
Maintenance of General Anesthesia	Patients greater than or equal to 2 months of age
Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients	Adults only



Approved Products Per Orange Book as of 06/24/2021

Mkt Status	Proprietary Name	Appl. No.	Dosage Form	Strength	RLD	RS	Applicant Holder	Approval Date
RX	DIPRIVAN	N019627	INJECTABLE	10MG/ML	RLD	RS	FRESENIUS KABI USA LLC	Jun 11, 1996
RX	PROPOFOL	A205067	INJECTABLE	10MG/ML			DR REDDYS LABORATORIES INC	Nov 15, 2018
RX	PROPOFOL	A077908	INJECTABLE	10MG/ML			HOSPIRA INC	Mar 17, 2006
RX	PROPOFOL	A205576	INJECTABLE	10MG/ML			INNOPHARMA LICENSING LLC A SUB OF PFIZER INC	Sep 16, 2020
RX	PROPOFOL	A075102	INJECTABLE	10MG/ML			SAGENT PHARMACEUTICALS INC	Jan 4, 1999
RX	PROPOFOL	A205307	INJECTABLE	10MG/ML			WATSON LABORATORIES INC	Dec 22, 2015
RX	PROPOFOL	A074848	INJECTABLE	10MG/ML			WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD	Apr 19, 2005
DISCN	PROPOFOL	A075392	INJECTABLE	10MG/ML			TEVA PARENTERAL MEDICINES INC	Sep 19, 2000
DISCN	DIPRIVAN	N019627	INJECTABLE	10MG/ML			FRESENIUS KABI USA LLC	Oct 2, 1989

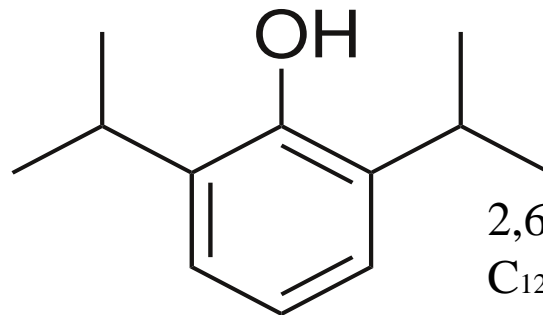


Propofol Injectable Emulsion Products, 10 mg/mL

- Propofol is slightly soluble in water
- The pKa is 11
- The octanol/water partition coefficient for propofol is 6761:1 at a pH of 6 to 8.5
- Drug Product is formulated in a white, oil-in-water emulsion
- Each drug product consists of propofol 10 mg/mL, soybean oil (100 mg/mL), glycerin (22.5 mg/mL), egg lecithin (12 mg/mL); and **Preservatives**; with sodium hydroxide to adjust pH
 - Preservative may be different

DIPRIVAN (Propofol) Injectable Emulsion Product (NDA 019627)

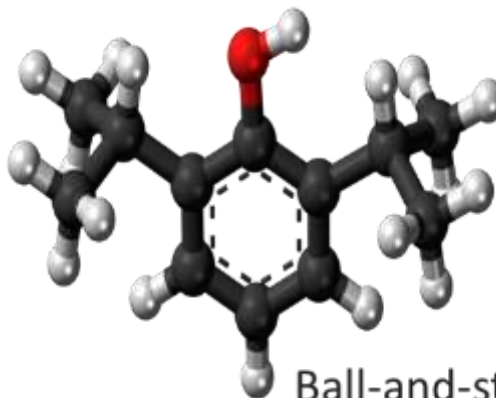
10 mg/mL, NDC 63323-269-XX



2,6-diisopropylphenol

$C_{12}H_{18}O$

MW 178.27



Ball-and-stick model of propofol

NDA 019627: How Supplied in the US



DIPRIVAN (propofol) Injectable Emulsion, USP Vials

Product No.	NDC No.	Strength	
260929	63323-269-29	200 mg per 20 mL (10 mg per mL)	20 mL ready-to-use single-patient infusion vial in packages of ten.
260950	63323-269-50	500 mg per 50 mL (10 mg per mL)	50 mL ready-to-use single-patient infusion vial in packages of twenty.
260965	63323-269-65	1,000 mg per 100 mL (10 mg per mL)	100 mL ready-to-use single-patient infusion vial in packages of ten.

Propofol undergoes oxidative degradation, in the presence of oxygen, and is therefore packaged under nitrogen to eliminate this degradation path.

Store between 4° to 25°C (40° to 77°F). Do not freeze. Shake well before use.

FDA Approved Labeling for Propofol Drug Products

DOSAGE AND ADMINISTRATION



- Strict aseptic technique must always be maintained during handling
- DIPRIVAN or Propofol Injectable Emulsion is a single access parenteral product (single patient infusion vial), which contains 0.005% disodium edetate (EDTA) or other preservatives to inhibit the rate of growth of microorganisms, for up to 12 hours, in the event of accidental extrinsic contamination.
- DIPRIVAN or Propofol Injectable Emulsion can still support the growth of microorganisms, as it is not an antimicrobially preserved product under USP standards. Do not use if contamination is suspected. Discard unused drug product as directed within the required time limits.

FDA Approved Labeling for Propofol Drug Products

DOSAGE AND ADMINISTRATION



Handling Procedures

- There have been reports in which failure to use aseptic technique when handling DIPRIVAN or Propofol Injectable Emulsion was associated with microbial contamination of the product and with fever, infection/sepsis, other life-threatening illness, and/or death.
- There have been reports, in the literature and other public sources, of the transmission of bloodborne pathogens (such as Hepatitis B, Hepatitis C, and HIV) from unsafe injection practices, and use of propofol vials intended for single use on multiple persons.

Use Instruction

- Shake well before use.
- Do not use if there is evidence of excessive creaming or aggregation, if large droplets are visible, or if there are other forms of phase separation indicating that the stability of the product has been compromised.
- Slight creaming, which should disappear after shaking, may be visible upon prolonged standing.

An example of Vial and Carton Label for Generic Products

20 mL Single Patient Use Vial NDC 0069-0209-01

Propofol Injectable Emulsion, USP

200 mg/20 mL (10 mg/mL)

For Intravenous Administration

SHAKE WELL BEFORE USING

Rx only

LOT: BATCH NUMBER
EXP: EXPIRY DATE

STERILE, Nonpyrogenic
Store between 4 to 25°C (40 to 77°F). Do not freeze.
Usual Dosage: See package insert for dosage information.

• Use strict aseptic technique
Contains EDTA, which inhibits microbial growth up to 12 hours, discard within 12 hours of opening

Each mL contains Propofol 10 mg, soybean oil (100 mg/mL), glycerin (22.5 mg/mL), egg lecithin (12 mg/mL), and edetate disodium (0.005%) with sodium hydroxide to adjust pH.

Distributed by Pfizer Labs
Division / Pfizer Inc.
New York, NY 10017
MADE IN SWITZERLAND

61000015 F.71

Preservatives are provided on the Labels of Vial and Carton

Sterile, Nonpyrogenic
Store between 4 to 25°C (40 to 77°F). Do not freeze.
Usual Dosage: See package insert for dosage information.
Propofol Injectable Emulsion USP should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of surgical/diagnostic procedure.

Facilities for the maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.

Each mL contains Propofol 10 mg, soybean oil (100 mg/mL), glycerin (22.5 mg/mL), egg lecithin (12 mg/mL); and edetate sodium (0.005%); with sodium hydroxide to adjust pH.

• Use strict aseptic technique
• Contains EDTA, which inhibits microbial growth up to 12 hours, discard within 12 hours of opening

Propofol Injectable Emulsion, USP

200 mg/20 mL (10 mg/mL)

For Intravenous Administration

SHAKE WELL BEFORE USING

• Use strict aseptic technique
Contains EDTA, which inhibits microbial growth up to 12 hours, discard within 12 hours of opening

Pfizer Injectables

Rx only

Preservatives in Currently Approved Drugs



- EDTA 0.005%
- Sodium metabisulfite 0.25 mg/mL
- Benzyl Alcohol 1.5 mg/mL & Sodium Benzoate 0.70 mg/mL
- Benzyl Alcohol 1.0 mg/mL or 1.5 mg/mL
- Sodium Benzoate 1.0 mg/mL

Impact of Repackaging or Combining Propofol Drug Products



- Improper repackaging **or combining** may cause characteristics changes such as changes in physicochemical properties
- Improper repackaging **or combining** may negatively affect the safety and effectiveness of the drug product
 - Impurity level increases due to degradation of the drug product
 - Repackaging or combining sterile drug product are susceptible to contamination
 - Failure to properly manipulate sterile DP under appropriate aseptic conditions could introduce contaminants that could cause serious patient injury or death

Physicochemical and Stability Properties for Propofol Injectable Emulsion Drug Products Considered for Repackaging or Combining Propofol



- Appearance
- pH
- Types of Preservatives
- Container Closure System (CCS) and Package Sizes
- Stability Data
- Expiration Date
- In-use study
- Additional Attributes
 - Mean Globule Size
 - The percentage of fat residing in globules larger than 5 μm (PFAT5)

Enforcement Discretion Policy

- As a temporary measure, in the following circumstances, FDA does not intend to take action for certain violations regarding propofol drug products that are within expiry and in their original containers:
 - The repackaged or combined drug product is provided directly to a hospital that informs the pharmacy (including a hospital or health system pharmacy) or outsourcing facility that it (a) is treating patients with COVID-19, and (b) has made reasonable attempts to obtain adequate supplies of an FDA-approved drug product in clinically appropriate presentations and has been unable to do so (III.1)

Enforcement Discretion Policy (Cont'd)



- In all cases, the repackaged or combined product is discarded if there is any change in appearance such as color, visible separation of the water and oil occurs such as the formation of any visible oil droplets or particulate matter (III.2)
- The product is repackaged or combined consistent with the practices described in the Repackaging Guidance **except that**, with respect to (1) combining products, (2) the application of a beyond-use-date (BUD), (3) product labeling, and (4) container closures. (III.3), the pharmacy or outsourcing facility proceeds as follows:
 - FDA-approved propofol products may be repackaged or combined without doing so under nitrogen (III.3.a)
 - Propofol should be mixed using aseptic technique under ISO 5 conditions whenever possible
 - This provides flexibility during public health emergency with limited time period preceding use of repackaged product

Enforcement Discretion Policy (Cont'd)



- When a drug product is prepared by placing FDA-approved propofol products into a new container, and the preservatives and antioxidants listed in the DESCRIPTION sections of the approved products' labeling match, a BUD of **not more than 12 hours** is used and the resulting product is NOT frozen ((III.3.b)
 - Different lots of propofol from the same manufacturer may be mixed under certain circumstances
- If there is a difference in preservative or antioxidant components, the two products are not combined except as follows. ((III.3.c)
 - A077908, A205067, and A205307 contain very similar preservative combinations, and the Agency believes it is low risk to combine them under the public health emergency
 - Mixed product of A077908, A205067, and A205307 will result in a final mixture with slightly less benzyl alcohol than has been demonstrated to be an effective antimicrobial preservative system. This mixture should be used as close to preparation time as possible and discarded **after 4 hours** as a precaution against microbial growth in the presence of reduced preservative content
 - Propofol products under NDA 019627 and ANDA 075102 are not combined with any other propofol product (more significant differences in preservatives)

Enforcement Discretion Policy (Cont'd)



- The container into which the drug product is repackaged or combined is suitable for storage of the drug product through its BUD. (III.3.d)
 - The active ingredient in propofol drug products may adsorb into certain plastic and rubber packaging components. While this is not a safety issue, it may impact efficacy.
- The labeling for the repackaged or combined drug product specifies: (III.3.e)
 - Store between 4° to 25°C (40° to 77°F). Do not freeze
 - The tubing and any unused portions of the propofol injectable emulsion should be discarded after [insert time and date that corresponds to the BUD]

Enforcement Discretion Policy (Cont'd)



- The drug product is otherwise repackaged or combined consistent with the conditions described in the Repackaging Guidance. (III.4)
 - For Pharmacy/Facility and Labeling
 - Not covered in this presentation

Appendix A in Guidance



	A	B	C	D	E
Manufacturer/ application number	Fresenius Kabi (NDA 019627)	Sagent Pharmaceuticals (ANDA 075102)	Hospira, Inc. (ANDA 077908)	Dr. Reddy's Laboratories (ANDA 205067)	Watson Laboratories, Inc. (ANDA 205307)
NDCs ¹⁸ of applicant	63323-269- XX; 65219- 800-XX	25021-608-XX	0409-4699-XX	43598-265- XX; 43598- 548-XX; 43598-549- XX	0591-2136-XX
Labeler/NDC	RX Pharma- Pack, Inc.: 49836-025-09; 49836-024-10		General Injectables and Vaccines, Inc: 52584-699-33		A-S Medication Solutions: 50090-4569-1
Labeler/NDC			HF Acquisition Co LLC, DBA HealthFirst: 51662-1471-1		General Injectables & Vaccines, Inc: 52584-098-55
Labeler/NDC			HF Acquisition Co LLC, DBA HealthFirst: 51662-1293-1 (20 mL)		
Labeler/NDC			HF Acquisition Co LLC, DBA HealthFirst: (100 mL) 51662-1470- 1		

Appendix A in Guidance (Cont'd)



	A	B	C	D	E
Manufacturer/ application number	Fresenius Kabi (NDA 019627)	Sagent Pharmaceuticals (AND 075102)	Hospira, Inc. (ANDA 077908)	Dr. Reddy's Laboratories (ANDA 205067)	Watson Laboratories, Inc. (ANDA 205307)
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Labeler/NDC			HF Acquisition Co LLC, DBA HealthFirst: 51662-1471-1		General Injectables & Vaccines, Inc: 52584-098-55
Labeler/NDC			HF Acquisition Co LLC, DBA HealthFirst: 51662-1293-1 (20 mL)		
Labeler/NDC			HF Acquisition Co LLC, DBA HealthFirst: (100 mL) 51662-1470- 1		

Repackage or Combine Propofol Drug Product (DP) Procedure

To repackage or combine consistent with the policy:

- Products that are included in the same column of this table may be prepared and given a Beyond Use Date (BUD) of not more than 12 hours (III.3.b for same Preservative).
- Propofol DP in Column A and Column B are not to be combined with a propofol drug product in any column other than its own.
- Propofol drug products in columns C, D, or E may be combined with a BUD of not more than 4 hours (III.3.c for Similar Preservatives).

Challenge Question #1



What are the FDA-Approved Indications for Propofol Injectable Emulsions?

- A. Antibacterial
- B. Antivirus
- C. Anti-inflammatory
- D. Anesthesia and Sedation

Challenge Question #2



Up to how many hours are the Preservatives in Propofol Injectable Emulsion expected to inhibit the rate of growth of microorganisms in the event of accidental extrinsic contamination?

- A. 4 hours
- B. 10 hours
- C. 12 hours
- D. 24 hours

Summary

- Discussed the temporary policy for repackaging or combining as described in the Guidance to address the COVID-19 public health emergency
- Evaluated quality information relevant to repackaging or combining propofol drug product
 - Labeling and storage conditions
 - Formulations
 - Physicochemical properties
 - Stability data of approved propofol products

Acknowledgement



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Thank You!

I will be back to answer questions
on the Panel