

Systematic Review - Meta Analysis

Systematic Literature Review on Sterile Injectable Dates of Use, Stability and Implications for Use

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ABSTRACT

Background: Beyond-use date (BUD) is crucial for the stability of injectable preparations. However, there is a knowledge gap and a lack of information regarding BUD determination in injection preparations. Therefore, a systematic review is needed to address the BUD of injection preparations. **Objective:** This study aimed to provide comprehensive insights into the stability, BUD data, and associated implications for injectable preparations through a systematic literature review approach. **Methods:** This study employed a systematic literature review guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The inclusion criteria were research articles from national and international journals discussing the BUD of sterile injection preparations published in the last 10 years. **Results:** Fourteen of the 19 articles related to BUD were selected for analysis. The analysis revealed that the stability of the 19 sterile injection preparations was significantly influenced by the characteristics of the preparation, storage conditions, and type of drug. These factors substantially affect the effectiveness and safety of drugs. Intravenous sterile injections involve several critical steps to ensure the safety and efficacy of the medications used. Adhering to BUD guidelines for intravenous injections is crucial for maintaining drug quality, which can help prevent infections or adverse reactions in patients. **Conclusion:** The stability of sterile injection preparations, which is influenced by various factors, has direct implications for BUD determination. The potential impacts of noncompliance with BUD for sterile injection preparations include product damage, sediment formation, color changes, precipitation, and chemical degradation, as well as increased safety risks, decreased drug effectiveness, and uncertainty in dosing when used. This review highlights the importance of considering these factors when determining BUD to ensure patient safety.

KEYWORDS

Drug stability, patient safety, sterile injectable, dates of use, quality control, drug storage

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INTRODUCTION

Approximately one in ten patients experienced harm during treatment due to medication errors. According to data from the World Health Organization (WHO), more than three million deaths occur annually due to unsafe care practices. Key adverse events with significant implications for patient safety include medication errors, unsafe surgical procedures, healthcare-associated infections, diagnostic errors, patient misidentification, unsafe blood transfusions, and venous thromboembolism [1]. Notably, over 50% of these injuries (one in 20 patients) are preventable, with half being attributable to medication-related incidents [2,3].

One such adverse event that poses a risk to patient safety involves medication errors and potential infections arising from inadequate information regarding the Beyond-Use Date (BUD) of injectable preparations [4]. An observational study across five hospital pharmacies in the US over a 5-day period revealed that parenteral nutrition (PN) solutions had the highest error rate, with an overall mean error rate of 9% for compounding intravenous (IV) preparations. Another study conducted at a teaching hospital reported that approximately 34% of medication errors in critical care units were linked to the compounding of IV preparations [5,6].

Sterile preparations play an important role in treatment, particularly in situations requiring intensive care, such as severe infections or chronic conditions. One form of sterile preparation is injection, which involves the injection of substances through the skin or other external tissue boundaries. In injection preparations, the active substance flows directly into systemic blood vessels or body tissues [7,8]. In healthcare practice, sterile preparations often undergo a compounding process, which includes combining, mixing, diluting, and repackaging [9]. Ensuring stability and sterility are crucial during the compounding process. A key concept related to the stability of injection preparations after compounding is the second-use date (BUD).

BUD is the time limit for using a drug after its primary packaging has been opened or after it has undergone a compounding process [10]. Determining the BUD for injection preparations is important because those that have undergone reconstitution generally exhibit lower stability than those that have not. Additionally, preparations used for injection must consider stability to avoid serious effects on the body's systems. Several factors affect the BUD of injection preparations, including the type of container, storage temperature, light exposure, and sterilization method. Stability parameters commonly evaluated in sterile injectable preparations include visual or organoleptic assessments along with degradation testing via tools such as high-performance liquid chromatography (HPLC). These checks help to detect problems such as physical damage, sediment formation, color changes, precipitation, or chemical degradation, which can pose safety risks, reduce drug efficacy, and cause dosage uncertainty during administration.

Despite this, there remains a gap in the knowledge regarding the determination of BUD in injection preparations and the implications of their use. The lack of studies specifically addressing the physicochemical and microbiological stability of sterile injection preparations poses challenges in the determination of BUD. This systematic review aims to collect information from the existing primary literature to address these gaps. The determination of BUD on the basis of the stability data of sterile injectable preparations can help reduce potential adverse effects, such as undesirable reactions, following the administration of reconstructed injectable products. This process can indirectly improve the quality and safety standards of these preparations.

This systematic review compiled information from the primary literature, focusing on the determination of BUD from stability data and its potential implications for sterile injectable preparations. The collected data on these implications can be valuable for pharmaceutical practitioners, the pharmaceutical industry, and health regulators in developing appropriate guidelines for establishing BUD, ensuring consistent quality standards across similar preparations, and reducing variability in handling and storage practices. Furthermore, this approach is essential for minimizing the risk of degradation of sterile injectable preparations after reconstruction, which is crucial for ensuring patient safety.

MATERIALS AND METHODS

Search strategy and criteria

The literature search used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method to filter out articles relevant to the topic under study [11]. The search was conducted via electronic databases, such as PubMed, ScienceDirect, EBSCO, and SAGE Journals. The keywords used included (1) sterile preparation AND Beyond-Use Date; (2) Sterile AND Beyond-Use Date; (3) Sterile injection AND Beyond-Use Date; (4) Injection AND Beyond-Use Date; (5) Parenteral AND Beyond expiration date; (6) Injection AND Beyond expiration dates; (7) Infusion AND Beyond expiration date; (8) Vial AND Beyond-Use Date; (9) Intravenous AND Beyond-Use Date AND BUD; (10) Injection AND Beyond-Use Date AND BUD; (11) Infusion AND Chemical AND Physical AND Compatibility; (12) Parenteral AND Beyond-Use Date; and (13) Beyond-Use Date AND sterile compound.

The eligible literature for this review includes national and international journals, as well as scientific research articles that specifically discuss BUD for sterile injectable preparations, focus on its determination and stability, and have been published within the last ten years (2015–2024). Articles that did not meet these criteria or exclusion criteria, particularly those in the form of reviews, guidelines, or magazine articles, as well as those published outside the specified timeframe, were excluded.

Literature compilation, data extraction and management

The literature was compiled via the Mendeley platform as a reference manager, compiling full-text articles that met the inclusion and exclusion criteria to facilitate data management and library organization. Articles that met the inclusion and exclusion criteria were analyzed and organized into data presentations containing information on the stability of sterile injection preparations, BUD data for each preparation, and implications related to those preparations. The relevant articles were identified by searching several databases via specific keywords. The initial screening was based on titles and abstracts, and only those that met the criteria were selected for further review. A more detailed evaluation was then conducted by analyzing the full content of the selected articles. The screening process leading to data extraction is shown in the PRISMA flow diagram. Data from all selected articles were subsequently extracted via a structured template in Microsoft Excel, with a focus on the key aspects of the study.

RESULTS

Article characteristics

On the basis of a literature review of BUD from several articles, 14 articles met the inclusion criteria out of a total of 19 selected from 1675 search results in the databases used (Figure 1). Additionally, 5 articles did not meet the inclusion criteria. The data from the literature search are displayed in the flowchart and distribution diagram of the inclusion criteria (Figure 2).

Stability data in sterile injection preparation

Data from the review of the articles were organized into several tables, each containing different information relevant to the topic of BUD. The stability of sterile injection preparations, as indicated by physical and chemical changes, also influences BUD. The stability of each sterile injection preparation is shown in Table 1.

Determination of the BUD for sterile injection preparation

The stability data of each drug studied in several articles influenced the determination of the beyond-use date (BUD) for sterile injection preparations. The determination of BUD was adjusted according to the USP < 797 > Pharmaceutical Compounding–Sterile Preparation guidelines (Table 2). The BUD values for each injection preparation obtained from the literature review are listed in Table 3.

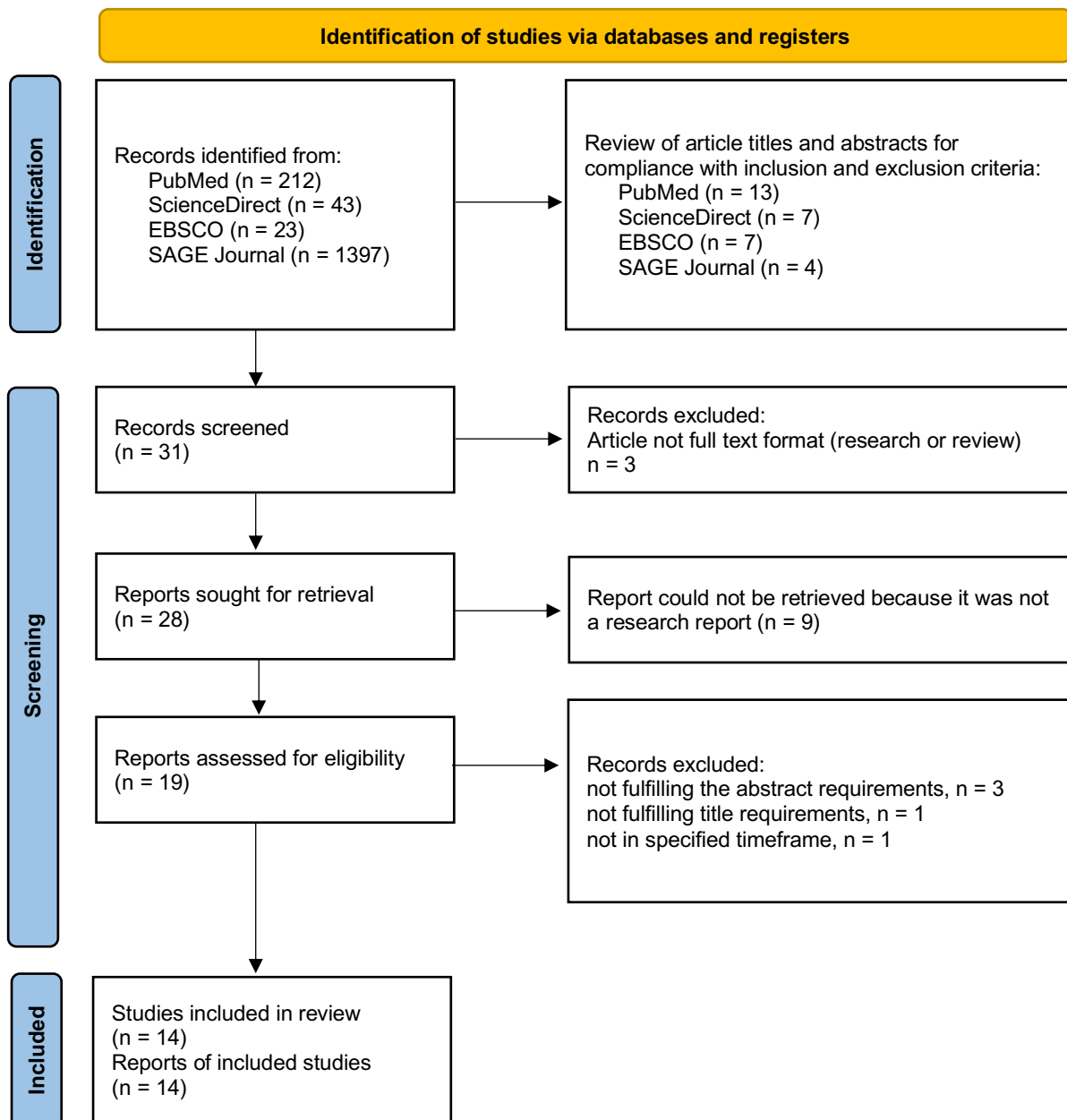


Figure 1. Flowchart systematic literature review

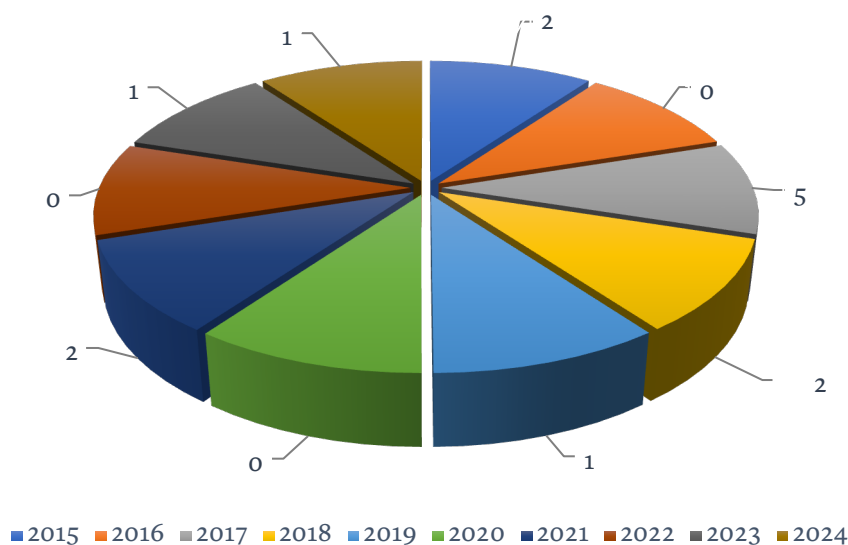


Figure 2. Distribution of articles from the last ten years (2015-2024) regarding BUD

Table 1. Stability data in sterile injection preparation

Drug name	Concentration	Solvent	Storage Container	Sampling Time Point	Stability Test Parameters	Result	Ref.
Sodium Phosphate	30 mmol/L (250 mL) and 150 mmol/L (100 mL)	D5W and NS	PVC	Days 0, 2, 7, 9, 16, 21, 23, 28, 30, 35, 50, and 63	Color change, particles or precipitates	Sodium phosphate solutions with concentrations of 30 and 150 mmol/L, whether stored in 5% dextrose in water (D5W) or 0.9% sodium chloride (NS), can maintain more than 94% of their initial concentrations over 63 days at 4°C or 23°C. The study showed that the solutions were chemically and physically stable, with no significant changes in appearance or concentration of active ingredients during the 63-day observation period	[12]
Glutamate-aspartate cardioplegia additive solution (GACAS)	58 mmol glutamate and 58 mmol aspartate in 250 mL	WFI	PVC (DEHP-free) and PVC (with DEHP)	Months 0,1, and 2	Measurement of pH, visual inspection (color, clarity, particulates), potency, and product degradation by HPLC	After 2 months of storage at cold temperatures (2°C-8°C), there was no significant change in pH (remaining approximately 7.00) or visual appearance for all stability samples. HPLC results showed the samples maintained 101% to 103% of the labeled strength for both amino acids, glutamate, and aspartate, by month 2. Initially, the stability was measured at 102%, then by months 1 and 2, there was a 1% decrease but still within the range of 101-103%	[13]
Parenteral Nutrition*	10-500 mg/mL	WFI	Vials	Hours 6, 18, 22, and 24	Sterility assessment (contamination indicated by turbidity or particles in the growth medium)	Single-dose vials containing parenteral nutrition therapy connected to an Automated Compounding Device can remain sterile for up to 24 hours when accessed and maintained in an ISO Class 5 clean environment at room temperature (20-25°C)	[14]

Drug name	Concentration	Solvent	Storage Container	Sampling Time Point	Stability Test Parameters	Result	Ref.
Cytarabine Fluorouracil Gemcitabine Ifosfamide	100 mg/mL 50 mg/mL 100 mg/mL 50 mg/mL	WFI	CSTD Vial Adaptor	Hours 0, 24, 48, and 72	HPLC analysis (comparing peak area and p value of test group vs control group)	The drug maintained chemical stability for up to 72 hours after being accessed using a Closed System Transfer Device at temperature ranges of 20°C–25°C and 30°C–35°C	[15]
Ertapenem	100 mg/mL	NS	Glass vial and polypropylene syringe	Days 0, 1, 2, 4, 7, 11, 14, and 18	Visual inspection (color change, presence of particles), and degradation products by HPLC	Ertapenem solution at a concentration of 100 mg/mL stored in the manufacturer's glass vials or polypropylene syringes retains more than 90.5% of its initial concentration when stored for 48 hours at 4°C and for an additional 1 hour at room temperature (23°C).	[16]
Durvalumab	50 mg/mL	WFI	Vial	Days 0, 7, and 14	Visual inspection, turbidity, submicronic aggregation, pH, osmolality, aggregation or fragmentation by SE-HPLC, charge distribution by IEX- HPLC	Durvalumab solutions remain physicochemically and microbiologically stable for at least 14 days when handled aseptically and stored at 4°C or room temperature (25°C). The results show that the remaining vials of durvalumab can be used for more than 24 hours.	[17]
Vinflunine (VFN)	0.75 and 1.54 mg/mL	NS and 5% glucose	Polyolefin infusion bag	Days 0, 1, 2, 3, 4, 5, 6, 7, 8, and 9	Visual inspection (color change and turbidity), gravimetric control (volume loss), pH, and product degradation by HPLC	The solution is stable for 2 days at room temperature (25.4 ± 0.7°C) and at least 7 days in the refrigerator (4.1 ± 0.5°C). Days 8-9 showed a color change, indicating degradation	[18]

Drug name	Concentration	Solvent	Storage Container	Sampling Time Point	Stability Test Parameters	Result	Ref.
Protein Piggyback Infusion	0.05 to 2.0 mg/mL	NS, WFI, and 0.45% NaCl	Glass vials, IV bags, syringes, and syringe infusion lines	24 hours	Visual inspection, turbidity, protein concentration and purity by RP-UPLC, invisible particle count by light obscuration	Mixtures with concentrations between 0.05 to 2.0 mg/mL have been shown to be compatible with WFI and administration materials, such as IV bags, syringes, and syringe infusion lines, for at least 24 hours at room temperature (25°C) and refrigerated (2-8°C)	[19]
Ranitidine Hydrochloride	5 mg/mL and 25 mg/mL	NS	Glass vial and polypropylene (PP) syringe	Days 0, 7, 14, 28, 56, and 91. Additional samples were collected at 6 months, specifically at months 6, 9, and 12	Visual inspection (color changes and clarity, pH, and product degradation by HPLC)	The solutions did not show significant changes in pH or clarity. Although some samples turned yellow, this was not associated with a decrease in concentration. The 25 mg/mL solution retained over 98.6% of its concentration for 6 months, while the 5 mg/mL solution maintained over 93.5% of its concentration for 91 days under all storage conditions, including room temperature (25°C) and refrigeration (5°C).	[20]
Sildenafil**	1.6 mg/mL	5% dextrose	Glass vial	Days 0, 1, 2, 3, 4, 5, 7, 9, 12, 14, 21, and 30	Visual inspection (color change and precipitation), and product degradation by HPLC	Sildenafil injection in 5% glucose remained effective at >90% after 30 days of storage at both room temperature and refrigeration. However, when sildenafil was prepared with heparin and dopamine, it retained less than 90% effectiveness after 3 days of storage at room temperature (20.5–21.1°C) and 21 days in the refrigerator (4.6–4.9°C)	[21]
Dexamethasone Sodium	0.08 and 0.4 mg/mL	NS and 5% glucose	PVC	Days 0, 1, 3, 7, and 14	Visual inspection (color change, clarity, microbial	During 14 days of storage at room temperature or in the refrigerator (2°C–8°C), no significant changes were	[22]

Drug name	Concentration	Solvent	Storage Container	Sampling Time Point	Stability Test Parameters	Result	Ref.
Phosphate (DSP)					growth, particulates), and product degradation by HPLC	observed in visual appearance. The pH of all samples stayed within one pH unit of the initial value. HPLC results confirmed that all samples maintained drug concentration between 94% and 100%, with no significant degradation products detected. Additional testing was performed at the end of storage at room temperature (20°C-23°C)	
Ibuprofen lysine	1.25 and 5 mg/mL	WFI	Polypropylene syringe	Minutes 0, 30, 1 hour, 4 hours, and 24 hours	Visual inspection (color change and precipitation), microscopic examination, pH, particle diameter and zeta potential determination by dynamic light scattering (DLS), and product degradation by HPLC	Ibuprofen lysine remained stable for 24 hours in a polypropylene syringe at room temperature (23°C)	[22]
del Nido Cardioplegia Solution (dNCS)	Sodium bicarbonate 1 mEq/mL, mannitol 20%, lidocaine 1%, magnesium sulfate 50%, and potassium chloride 2 mEq/mL	Plasma-Lyte A, 1000 mL	Ethylene vinyl acetate (EVA)	Day 0 to Day 30	Visual inspection (color change, clarity, precipitation), pH, and testing by HPLC and mass spectrometry (LC/MS)	del Nido Cardioplegia Solution (dNCS) remained stable for at least 30 days when stored in ethylene vinyl acetate (EVA) at refrigerated temperature (4°C), while under conditions of 70°C and 80% relative humidity in an environmental chamber, the solution was not stable for up to 30 days	[23]

Drug name	Concentration	Solvent	Storage Container	Sampling Time Point	Stability Test Parameters	Result	Ref.
Digoxin	0.05 mg/mL	NS	Glass vial	Days 0, 14, 30, 60, 90, 120, 150, and 180	Organoleptic changes, degradation products by HPLC with ultraviolet detection, and particulate matter test with a particle counter	Digoxin concentration remained above 90.0% of its initial concentration throughout the 180 days of the study. No organoleptic changes were observed, particulate assessments were within acceptable limits, and sterilization specifications were met. Digoxin at a concentration of 0.05 mg/mL, prepared by diluting 0.25 mg/mL digoxin with normal saline (NS), remained stable for at least 180 days at room temperature (25°C) and refrigeration (5°C)	[24]

Remarks: Data tabulation and extraction in this study were done manually by the authors by reviewing each selected paper. NS = normal saline; WFI = water for injection; D5W = 5% dextrose in water.

*Parenteral nutrition contains ascorbic acid 500 mg/mL, calcium gluconate 0.485 mEq/mL, famotidine 10 mg/mL, infuvite adult 100 mL, magnesium sulfate 4 mEq/mL, potassium acetate 2 mEq/mL, potassium chloride 2 mEq/mL, potassium phosphate 3 mmol/mL, sodium acetate 2 mEq/mL, and sodium chloride 23.4%, **Sildenafil in combination with heparin and dopamine.

Table 2. Determination of the BUD for sterile preparation according to the USP

Preparation Characteristics			Storage Conditions	
Method of Compounding	Sterility Test Performed and Passed	Controlled Room Temperature	Refrigerator (2°-8°)	Freezer (-25° to -10°)
Aseptically processed CSPs	No	Prepared from one or more non sterile starting component(s): 1 day	Prepared from one or more non sterile starting component(s): 4 day	Prepared from one or more non sterile starting component(s): 45 day
	Yes	Prepared from only sterile starting component(s): 4 day	Prepared from only sterile starting component(s): 10 day	Prepared from only sterile starting component(s): 45 day
Terminally Sterilized CSPs	No	30 days	45 days	60 days
	Yes	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

Remarks: USP, The United States Pharmacopeial Convention Inc.

Table 3. BUD of sterile injection preparation

Drug Name	Route of Administration	BUD (Beyond Use Date)			Ref.
		Controlled Room Temperature (20-25°C)	Refrigerator (2-8°C)	Additional Treatment	
Sodium Phosphate	IV	2 days (48 hours)	14 days	Without fluorescence light protection	[12]
Glutamate-Aspartate Cardioplegia Additive Solution (GACAS)	IV	NE	2 months	NA	[13]
Parenteral Nutrition	IV	6-24 hours	NE	Connected to an Automated Compounding Device (ACD)	[14]
Cytarabine Fluorouracil Gemcitabine Ifosfamide	IV	3 days	NE	Use CSTD system	[15]
Ertapenem	IV	5 hours 30 minute	2 days (48 hours)	Without fluorescence light protection	[16]
Durvalumab	IV	7 days	14 days	Protected from sunlight	[17]
Vinflunine (VFN)	IV (infusion)	2 days	7 days	Exposed to ambient light and Protected from light	[18]
Protein Piggyback Infusion	IV (infusion)	24 hours	24 hours	Various container in IV bags, syringes, and syringe infusion lines	[19]
Ranitidine Hydrochloride (25 mg/mL dan 5 mg/mL)	IV	6 months (25 mg/mL); 91 days (5 mg/mL)	6 months (25 mg/mL); 91 days (5 mg/mL)	Protected from light and exposed to light	[20]
Sildenafil	IV	3 days	21 days	NA	[25]
Dexamethasone Sodium Phosphate (DSP)	IV	14 days	14 days	NA	[21]
Ibuprofen lysine	IV	24 hours	NE	Container in Polypropylene syringe	[22]
del Nido cardioplegia solution (dNCS)	IV	<30 days	30 days	Exposed to light	[23]
Digoxin	IV	180 days	180 days	Protected by light	[24]

Remarks: NE = not explained; NA = not available; all BUD based on preparation method of aseptically processed.

Implications of the BUD for sterile injection preparation

The BUD is determined to avoid potential issues that may arise from errors in usage, preparation methods, or other factors. Some of the implications that may result from incorrect BUD or preparation factors are presented in Table 4.

Table 4. Implications of BUD sterile injectable preparation

Drug Name	Implication	Ref
Parenteral Nutrition	Frequently exchanged vials can increase the amount of handling and risk of contamination. Involvement of many personnel increases the risk of touch contamination.	[14]
Vinflunine (VFN)	Should only be administered intravenously. VFN can cause venous irritation.	[18]
Ranitidine Hydrochloride	Waste of raw materials, product damage, precipitate formation, and color changes.	[20]
Sildenafil	In practice, it is impossible to mix all three components (sildenafil, heparin, dopamine) effectively	[25]
Dexamethasone Sodium Phosphate (DSP)	Significant pH changes in DSP IV mixtures can increase oxidation and hydrolysis. Dilute solutions are more prone to drug loss due to absorption into packaging materials.	[21]
Ibuprofen Lysine	TPN electrolyte is incompatible with ibuprofen lysine, forming a precipitate. However, Intralipid remains stable without precipitate or phase separation when mixed.	[22]
del Nido cardioplegia solution (dNCS)	If incompatibility occurs, it may fail to minimize electrolyte shifts across the myocardial cell membrane, particularly for calcium, impacting postreperfusion effects.	[23]
Digoxin	Administering adult formulations to young children is dangerous due to difficulty in measuring small doses, especially in low-weight infants. Digoxin is a high-alert drug.	[24]

DISCUSSIONS

The second-use date (BUD) is the effective time limit for ensuring the stability of a drug preparation after its primary packaging has been opened for consumption or if the packaging has been damaged. The determination of BUD is influenced by factors such as humidity, temperature, sunlight exposure, microbial contamination, and storage conditions in the mixing area. BUD is a critical factor that must be considered and included in primary drug packaging to ensure that the public uses medications more cautiously. This is essential because BUD helps guarantee the safety and effectiveness of drug preparations once they have been opened. Additionally, BUD reduces the risk associated with the use of unstable drugs, which may lead to side effects [26].

Of the 19 articles searched via keywords related to Beyond-Use Date (BUD), only 14 met the inclusion criteria and were considered for this review. The main inclusion criterion for this review focused on the stability data of sterile injectable preparations that influence the determination of BUD. Additional criteria include articles discussing stability data, BUD information, and implications for preparations. However, some studies have not addressed the implications of the tested preparations. For example, Shi et al. [19] reported only the stability parameters tested in the preparation (Protein Piggyback Infusion), such as compatibility when mixed with water for injection (WFI) and used in IV bags, syringes, and infusion lines for at least 24 h at room temperature (25°C) and cold temperatures (2–8°C), without mentioning the implications of degradation or stability issues. Moreover, some articles provide BUD data under a single condition, which contrasts with the recommendations of the USP. For example, Garcia et al. [22] reported only the BUD of the preparation at room temperature (25°C) without evaluating it at cold temperatures (2–8°C). This presents a limitation in the literature review, as several primary studies lack comprehensive information on the BUD of sterile injectable preparations, particularly concerning the stability data and their implications.

The results obtained from the article review presented data on the stability of preparations, which have implications for BUD and the consequences of using drugs beyond their specified BUD limits. The preparations discussed are sterile preparations, which are particularly at risk if misused. One commonly used preparation is sterile injection, the majority of which is administered intravenously (IV). Intravenous sterile injections involve several critical steps to ensure the safety and efficacy of the medications used. Adhering to BUD guidelines for intravenous injections is crucial for maintaining drug quality, which can help prevent infections or adverse reactions in patients [10].

Drug stability is a crucial factor to consider when injection preparations are used. As indicated in Table 1, the determination of the second-use date (BUD) significantly affects the stability of a drug after compounding or when the primary packaging is opened or damaged. The test parameters used to assess the stability of sterile injection preparations include monitoring changes in drug components, such as color and clarity, pH, the presence of particles or sediment, crystallization, degradation, and volume loss. Throughout the testing period, the stability of each drug preparation decreased over time, with stability data from the final testing day reported in each article reflecting the BUD of the tested preparation. Factors such as testing duration, storage conditions, and containers used can affect the quality of the preparation, indicating whether they were made according to applicable standards.

Rapid degradation or damage to the preparation suggests that the sterile injection preparation does not meet the required quality standards, as evidenced by the BUD determined during stability testing. Some test results indicated that BUD values extended beyond one month, accompanied by good chemical stability data that did not exceed the limits specified by the United States Pharmacopeia (USP). These findings suggest that certain sterile preparations can achieve longer BUDs if sterility testing is validated for each batch of prepared drugs [10]. In addition, the determination of BUD for sterile injectable preparations can be based on the expiration date (ED) of the product. BUD should not exceed the earliest date set by the expiration date, which is determined by the chemical and physical stability of the preparation. In addition, BUD is influenced by the risk of microbial contamination due to prolonged storage or procedural errors during reconstruction. To establish a longer BUD, sterility testing must also be performed for certain preparations or batches [27].

The determination of the Beyond-Use Date (BUD) has been reported in several studies and references in the field. For example, Engel et al. [28] reported the BUD of various sterile preparations, which was determined on the basis of the specifications of ingredients listed in the pharmacopoeia, formulated immediately after opening, and aligned with the expiration date [28]. BUD applies only under the assumption that the mixture is prepared for a single patient and not for batch compounding. This determination also considers the physical and chemical stability of the preparation. If the information is limited to chemical stability, the BUD is set to match the expiration date of the preparation. The guidelines recommend that any sterile preparation requiring reconstruction should include safe compounding information provided in the "other information" section of the compounding container [29]. This section contains details on BUD after compounding, as well as information on the stability of the preparation [28–30].

Table 3 lists the second-use date (BUD) for sterile injection preparations, all of which were prepared via aseptic techniques with appropriate testing. In accordance with the USP guidelines, the stability of sterile injection preparations is defined as the ability of a product to maintain its properties and characteristics within specific limits during storage and use, indicating its shelf-life [20]. In accordance with the USP criteria, sterile injection preparations subjected to aseptic testing have vary BUDs according to storage conditions: 30 days at controlled room temperature (20–25°C), 45 days in a refrigerator (2–8°C), and 60 days in a freezer (-25°C to -10°C) [31]. The BUD reflects product stability, which directly impacts the safety and effectiveness of the medication. Among the 14 reviewed articles, most reported BUD results were consistent with the USP <797> guidelines, although two articles—by Fleming and Donnelly (2018) and Friciu et al. (2021)—reported inconsistencies with the BUD values listed in USP <797> for Pharmaceutical Compounding—Sterile Preparations (Table 2) [20,24,31].

Fleming and Donnelly [20] reported that ranitidine injection preparations were stable for six months when refrigerated under protected conditions and for 91 days at room temperature (25°C) when stored in a polypropylene syringe containing a 5 mg/mL ranitidine injection solution. Although BUD exceeded the time recommended by the USP, the concentration of the injection solution decreased significantly (>90%). This indicates that BUD exceeded the USP <797> guidelines, leading to potential product degradation, including decreased concentration, sediment formation after the 91-day period, and changes in color [20].

In a study by Friciu et al. [24], a mixed digoxin solution for injection was reported to be stable for at least 180 days when stored at both refrigerated and room temperatures. The compounding process, which utilized normal saline (NS) as a solvent with an aseptic testing method, revealed that the appearance of all digoxin samples remained consistent throughout the study, indicating no detectable visual instability. The digoxin solution (0.05 mg/mL) was obtained by diluting a 0.25 mg/mL digoxin solution with normal saline or a commercial vehicle, and it remained stable for at least 180 days at both 5°C and 25°C. The lower limit of the 95% confidence interval for the predicted concentration at 180 d was not less than 90.0% for all conditions, thereby meeting the testing specifications [24]. However, this BUD exceeded the time stated in the USP <797>.

Variations in stability data, especially regarding the percentage of drug content in sterile injectable preparations that exceed the BUD set by the USP, are likely due to differences in reconstruction procedures. A study by Fadel et al. [32] reported that 77% of hospitals across several countries with sterile compounding facilities adhere to USP clean room requirements (USP <797>) when performing drug reconstruction. Additionally, the differences in stability were influenced by the properties of the compounds used. For example, digoxin is more stable, with higher bioavailability and longer half-life than ranitidine [33]. Therefore, even if the BUD of these preparations exceeds the USP criteria, the percentage of remaining active ingredients will differ between preparations. For sterile injectable preparations exceeding the BUD limits set by the USP or other guidelines, such as the ISMP or ASHP, either the maximum available BUD data should be followed or the expiration date (ED) should be adhered to before reconstruction [29,33].

The potential risks associated with noncompliance with the Beyond-Use Date (BUD) for digoxin solutions, classified as high-alert medications, include instability, such as precipitation and chemical degradation, with an increased risk of precipitation when normal saline solutions are used as opposed to commercial vehicles [24]. Furthermore, digoxin is typically administered to adults, making it challenging and potentially hazardous to administer adult formulations to young children, as the required injection volume is difficult to measure, particularly in low-birth-weight infants [24]. The extended BUD for digoxin solutions raises concerns regarding the administration of injectable formulations to children given the significant risk factors and potential adverse effects involved.

The use of drugs that exceed their second-use date (BUD) can generally increase safety risks, decrease drug effectiveness, and create uncertainty regarding dosing. This is especially true for sterile preparations, which typically have a relatively shorter BUD, as this can increase the risk of contamination and bacterial colonization, thereby posing a significant threat to patient safety. In Table 4, two articles report the implications of BUD for sterile injection preparations that are inconsistent with the BUD guidelines stated in the USP <797> for Pharmaceutical Compounding—Sterile Preparations. The study by Fleming and Donnelly [20] highlights possible implications, such as wasting raw materials due to damaged products, which is indicated by the formation of sediment and changes in color. In contrast, Friciu et al. [24] recommended conducting further stability studies because of the potential for instability, including precipitation and chemical degradation [20,24].

Given these implications, it is crucial to include BUD information on drug packaging to prevent adverse effects associated with drug preparations that do not meet BUD requirements. However, BUD are not always listed in drug product packaging, which underscores the importance of pharmacists communicating this information through drug information services to both patients and healthcare providers responsible for administering injection preparations. Pharmacists play a vital role in ensuring drug and patient safety. Therefore, it is essential for pharmacists to be well versed in the general provisions related to BUD, understand the stability of pharmaceutical

preparations, and know how to determine BUD for various drug products. In addition to providing information on BUD, pharmacists are also critical in compounding sterile injection preparations to maintain drug stability in accordance with the USP guidelines. Properly maintaining drug stability allows for an accurate BUD determination that adheres to established standards. Compounding sterile preparations requires specialized techniques and knowledge, as they are directly related to drug stability and the implications of using injection preparations after their primary packaging has been opened [30]. This finding is consistent with the research of Hutchinson et al. [14], which emphasized that the compounding of sterile injection preparations, including parenteral nutrition, must be conducted by qualified and trained pharmaceutical personnel. This is essential to minimize contamination and prevent waste of sterile injection drug ingredients.

Clinical recommendations

The review of Beyond-Use Date (BUD) in sterile injectable preparations yields several critical clinical recommendations. Healthcare practitioners should strictly adhere to the USP <797> guidelines when determining BUD for sterile preparations, particularly those that are maintained for 30 days at controlled room temperature (20–25°C), 45 days in refrigeration (2–8°C), and 60 days in freezer conditions (-25°C to -10°C) for aseptically processed preparations that have undergone sterility testing. Pharmacists should implement robust quality control measures during the compounding process, including regular monitoring of physical and chemical stability parameters such as pH, color changes, particle formation, and chemical degradation. Healthcare facilities should establish standardized protocols for handling and storing sterile injectable preparations, with particular attention given to high-alert medications, such as digoxin. Additionally, comprehensive documentation systems should be implemented to track BUD information, storage conditions, and any stability-related observations. Healthcare providers should ensure proper training of personnel involved in sterile compounding to minimize contamination risks and maintain product integrity throughout the preparation and storage period.

Limitations

This systematic review presents several notable limitations that warrant consideration. First, the review was restricted to articles published within the last ten years (2015–2024), potentially excluding relevant historical data on sterile preparation stability. The analysis was limited by incomplete reporting in some primary studies, particularly regarding the implications of stability issues and comprehensive BUD data across different storage conditions. Additionally, there was considerable heterogeneity in the methodologies used for stability testing across studies, making direct comparisons challenging. Some studies lacked data on microbiological stability, focusing primarily on chemical and physical stability parameters. The review also noted inconsistencies in adherence to the USP <797> guidelines across different healthcare settings, potentially affecting the generalizability of the findings. Furthermore, the research focused predominantly on hospital pharmacy settings, potentially limiting the applicability of findings to other healthcare contexts where sterile preparations are handled.

CONCLUSIONS

Sterile injection preparations made via aseptic methods, which include controlled room temperature (20–25°C), refrigeration (2–8°C), and freezing (-25°C to -10°C), differ in their use dates (BUD) depending on their storage conditions. A review of the articles indicates that the stability of the preparations, as evidenced by parameters such as pH, color changes, and degradation, does not compromise the concentration of the preparation as long as the BUD adheres to USP standards. Preparations with BUD that exceed the limits stated in USP <797>, such as ranitidine and digoxin injections, pose risks if used beyond their recommended time owing to potential concentration reduction linked to decreased stability. Noncompliance with BUD for these preparations can lead to product damage, sediment formation, color changes,

precipitation, and chemical degradation. Medications that surpass BUD are associated with increased safety risks, diminished effectiveness, and dosage uncertainty. Therefore, accurately determining and communicating BUD for various sterile injection preparations is crucial for ensuring patient safety.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors, Methodology: NPKSD, DJAP; Software: DJAP, LDS, IGAWPD, NLKW; Validation: DJAP, LDS, IGAWPD, NLKW; Formal analysis: LALNP, MDH, IGAAGSD; Investigation: LALNP, MDH, IGAAGSD; Resources: NKIR, DW, KAMS; Data Curation: NKIR, DW, KAMS; Writing - Original Draft: PAPS, NPRN, NPKSD, IGAAGSD; Writing - Review & Editing: all authors; Visualization: IGAAGSD; Supervision: NKW.

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