

RESEARCH MONOGRAPH . COMPOUND PROFILE

Bacteriostatic- Water

A sterile, nonpyrogenic preparation of Water for Injection preserved with 0.9 percent benzyl alcohol, serving as the standard multi-dose diluent and reconstitution vehicle for lyophilized peptides, proteins, and small-molecule injectables in pharmaceutical, compounding, and research applications.

DOCUMENT	KDC-MN-1547
ISSUED	2026-05-15
REVISION	1.0
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COMPOUND CLASS	Preserved sterile aqueous vehicle for parenteral reconstitution and dilution

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ABSTRACT

Bacteriostatic Water for Injection, USP is a sterile, nonpyrogenic aqueous preparation containing 0.9 percent (9 mg/mL) benzyl alcohol as a bacteriostatic preservative, manufactured to the United States Pharmacopeia monograph specification and distributed under FDA oversight as a pharmaceutical-grade parenteral vehicle. Unlike Sterile Water for Injection, which contains no antimicrobial agent and is designated for single-use applications, Bacteriostatic Water for Injection is formulated specifically for multi-dose access, permitting repeated aseptic puncture of a single vial over a period of up to 28 days while maintaining microbiological integrity. The preparation is classified as a pharmaceutical vehicle rather than an active pharmaceutical ingredient; it carries no intrinsic therapeutic activity and is indicated exclusively as a diluent or solvent for drugs intended for intravenous, intramuscular, or subcutaneous injection, according to the labeling of the drug to be administered.

The bacteriostatic property of the formulation derives entirely from the benzyl alcohol excipient, a simple aromatic primary alcohol ($\text{C}_6\text{H}_5\text{CH}_2\text{OH}$; CAS 100-51-6; molecular weight 108.14 g/mol) that exerts its antimicrobial effect principally through disruption of bacterial cell membrane phospholipid bilayer integrity and interference with cellular metabolic processes. The mechanism is bacteriostatic rather than bactericidal: at 0.9 percent concentration, benzyl alcohol inhibits the reproduction of common environmental contaminants (including *Staphylococcus aureus* and *Pseudomonas aeruginosa*) without achieving immediate sterilization of the solution. This distinction is

operationally important, as the formulation depends on initial sterility at the point of manufacture and on aseptic technique during use to maintain the sterile state; the preservative serves as a secondary barrier against microbial proliferation following vial puncture.

Benzyl alcohol is metabolized in adult humans through a well-characterized hepatic oxidation pathway: alcohol dehydrogenase converts benzyl alcohol to benzaldehyde, aldehyde dehydrogenase converts benzaldehyde to benzoic acid, and benzoic acid is conjugated with glycine in the liver to form hippuric acid, which is excreted renally. Within six hours of oral administration of 1.5 g of benzyl alcohol, adult subjects excreted 75 to 85 percent of the dose as urinary hippuric acid, reflecting the efficiency of this metabolic pathway in mature individuals. However, in neonates (particularly premature infants), the enzymatic capacity for benzoic acid metabolism is developmentally immature, and repeated parenteral exposure to benzyl alcohol at cumulative doses of 100 to 240 mg/kg/day has been associated with a severe toxicity syndrome characterized by metabolic acidosis, gasping respirations, central nervous system depression, intraventricular hemorrhage, and cardiovascular collapse, termed the "gasping syndrome." This association, first reported in 1982 in the New England Journal of Medicine and subsequently confirmed by the FDA, resulted in a regulatory contraindication against the use of benzyl alcohol-containing preparations in neonatal patients.

The preparation is supplied in multi-dose glass or plastic flip-top vials, most commonly in a 30 mL presentation. The principal FDA-listed manufacturer is Hospira, Inc. (a Pfizer subsidiary), with the product distributed under NDC codes including 0409-3977. The USP monograph specifies a pH range of 4.5 to 7.0, a bacterial

endotoxin limit of less than 0.5 USP Endotoxin Units per mL, and compliance with USP particulate matter, sterility, and container-closure integrity requirements. The preparation is isotonic and osmotically insufficient on its own and is not suitable for direct intravenous administration without prior dilution or reconstitution with the intended drug product; the tonicity of the final solution depends on the solute.

This monograph reviews the compound identification, history, molecular pharmacology (of the benzyl alcohol preservative), pharmacokinetics of benzyl alcohol, the preclinical and clinical evidence base for safety and toxicology, sourcing and quality verification considerations, reconstitution and handling protocols, interactions with peptide and protein solutes, the adverse event and safety signal profile (including neonatal contraindication), and a comparative assessment of five alternative parenteral vehicles against Bacteriostatic Water for Injection on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Pharmacopeial name: Bacteriostatic Water for Injection, USP.

Common abbreviations: BAC water, BW, BWFI.

Pharmacopeial classification: Pharmaceutical vehicle; sterile diluent for parenteral administration.

USP monograph: Bacteriostatic Water for Injection, United States Pharmacopeia, General Chapter and Official Monograph.

National Drug Code (NDC): 0409-3977 (Hospira/Pfizer, 30 mL multi-dose vial); additional NDC listings include 0409-1093 (alternative packaging configurations). Multiple generic manufacturers hold approved NDCs.

Regulatory status: Listed pharmaceutical product under FDA oversight. Not a controlled substance. Not an active pharmaceutical ingredient. Classified as a sterile vehicle or diluent excipient.

1.2 Composition and structural class

Bacteriostatic Water for Injection is a binary formulation consisting of two components:

Component 1: Water for Injection, USP. Purified water meeting the USP monograph for Water for Injection, produced by distillation or by validated equivalent purification methods (reverse osmosis with ultrafiltration) and meeting bacterial endotoxin specifications of less than 0.25 USP Endotoxin Units per mL prior to the addition of preservative. Chemical Abstracts Service registry number: 7732-18-5. Molecular formula: H₂O. Molecular weight: 18.015 g/mol.

Component 2: Benzyl alcohol, USP (preservative). Present at a concentration of 0.9 percent weight per volume (9 mg/mL). Chemical Abstracts Service registry number: 100-51-6. International Union of Pure and Applied Chemistry name: phenylmethanol. Molecular formula: C₇H₈O (alternatively written C₆H₅CH₂OH).

Molecular weight: 108.14 g/mol. Benzyl alcohol is a colorless liquid at room temperature with a mild aromatic odor, a melting point of negative 15.2 degrees Celsius, a boiling point of 205.3 degrees Celsius, and a density of 1.045 g/mL at 25 degrees Celsius. It is miscible with water in all proportions at the 0.9 percent concentration used in the formulation. The pKa is approximately 15.4, rendering the compound essentially non-ionized at all physiologically relevant pH values.

Final product specifications (USP monograph):

- pH: 4.5 to 7.0 (measured with 0.3 mL saturated potassium chloride per 100 mL specimen); typical measured pH is 5.7
- Bacterial endotoxins: less than 0.5 USP Endotoxin Units per mL
- Sterility: meets USP sterility test requirements
- Particulate matter: meets USP requirements for sub-visible particulate matter in injectable preparations
- Benzyl alcohol content: 0.9 percent w/v (assay range per manufacturer specification, typically 0.85 to 0.95 percent)

1.3 Synthesis and manufacture

The manufacture of Bacteriostatic Water for Injection proceeds in three principal stages under current Good Manufacturing Practice (cGMP) conditions:

Stage 1: Water for Injection production. Source water (potable municipal water or pretreated feedwater) is purified through a validated system typically comprising multimedia filtration, water softening, carbon adsorption, reverse osmosis (single or double pass), electrodeionization or mixed-bed deionization, and final distillation or ultrafiltration. The final water meets USP Water for Injection specifications including conductivity (less than 1.3 microsiemens per centimeter at 25 degrees Celsius), total organic carbon (less than 500 parts per billion), and bacterial endotoxins (less than 0.25 EU/mL). Production systems operate under continuous recirculation with periodic sanitization (hot water, ozone, or chemical) to prevent biofilm formation.

Stage 2: Formulation. Benzyl alcohol (USP or NF grade) is added to the Water for Injection at a target concentration of 0.9 percent w/v. The formulation is mixed under controlled conditions, sampled for pH and benzyl alcohol content by high-performance liquid chromatography or gas chromatography, and adjusted if necessary.

Stage 3: Fill, finish, and sterilization. The formulated solution is sterile-filtered through 0.22-micrometer membrane filters into pre-sterilized glass or plastic vials under aseptic conditions. Vials are sealed with elastomeric closures and aluminum crimp caps. Terminal sterilization by autoclaving may be applied depending on the container-closure system. The finished product is tested for sterility, bacterial endotoxins, particulate matter, pH, benzyl alcohol content, container-closure integrity, and appearance prior to release.

2. Abstract

Bacteriostatic Water for Injection, USP is the standard preserved aqueous vehicle for the reconstitution and dilution of lyophilized and concentrated pharmaceutical preparations intended for multi-dose parenteral administration. The formulation consists of Water for Injection preserved with 0.9 percent benzyl alcohol, a concentration established through decades of pharmaceutical practice as providing effective bacteriostatic activity against common environmental contaminants while maintaining compatibility with the majority of small-molecule drugs, peptides, and proteins encountered in clinical and research applications [1, 2].

The preparation occupies a defined position in the hierarchy of pharmaceutical waters. Water for Injection (WFI) is the base solvent, meeting the most stringent purity and endotoxin standards in the pharmacopeial system. Sterile Water for Injection (SWFI) is WFI that has been sterilized and packaged in single-dose containers without preservative; it is limited to single-puncture use. Bacteriostatic Water for Injection (BWFI) is WFI with added benzyl alcohol preservative, packaged in multi-dose containers, and permitted for repeated aseptic access over a maximum of 28 days from first puncture [1, 3]. Bacteriostatic Sodium Chloride for Injection (0.9 percent sodium chloride with 0.9 percent benzyl alcohol) provides isotonicity in addition to bacteriostasis. The selection among these vehicles is determined by the drug product labeling, the anticipated number of doses per vial, the tonicity requirements of the final solution, and patient population considerations (specifically, the neonatal contraindication for benzyl alcohol-containing preparations).

The clinical and research importance of the preparation is functional rather than pharmacological. Bacteriostatic Water for Injection has no intrinsic therapeutic activity. Its value lies in enabling the safe multi-dose use of reconstituted injectable preparations, reducing waste, simplifying dosing protocols for compounds requiring repeated subcutaneous or intramuscular administration (such as peptide hormones, growth factors, and research peptides), and providing a standardized, pharmacopeially defined vehicle that ensures batch-to-batch consistency in the diluent component of the final formulation [2, 4].

3. Discovery and Development History

3.1 Historical context of pharmaceutical water

The concept of sterile water for parenteral use evolved in parallel with the development of injectable therapeutics in the late 19th and early 20th centuries. The recognition that waterborne microbial contamination was a principal source of injection-related infection drove the development of increasingly stringent water purification and sterilization standards. The United States Pharmacopeia first established monograph standards for Water for Injection in the early 20th century, with progressive tightening of specifications for pyrogens (later replaced by the bacterial endotoxin test), conductivity, total organic carbon, and microbial limits [5].

3.2 Introduction of benzyl alcohol as a parenteral preservative

The use of antimicrobial preservatives in multi-dose injectable preparations emerged as a practical response to the operational need for vials that could be accessed multiple times without microbial proliferation in the interval between punctures. Benzyl alcohol was adopted as a parenteral preservative in the mid-20th century on the basis of its broad-spectrum bacteriostatic activity, low systemic toxicity in adults at the concentrations used, chemical stability in aqueous solution, compatibility with a wide range of drug substances, and minimal interference with analytical assays for active ingredients [6, 7].

The 0.9 percent concentration became the standard through empirical optimization. At concentrations below approximately 0.5 percent, antimicrobial efficacy against common contaminants (particularly *Pseudomonas* species) is inadequate for the 28-day multi-dose use period. At concentrations above approximately 2 percent, local tissue irritation at injection sites increases and compatibility with some protein therapeutics is compromised. The 0.9 percent concentration represents a consensus optimum that has been validated by decades of commercial pharmaceutical use and by USP antimicrobial effectiveness testing (USP Chapter 51) [6, 8].

3.3 The gasping syndrome and neonatal safety signal

The most significant safety event in the history of Bacteriostatic Water for Injection was the identification of the "gasping syndrome" in premature neonates in 1982. Gershanik et al. reported in the New England Journal of Medicine a series of neonatal deaths associated with the use of benzyl alcohol-preserved flush solutions in neonatal intensive care units [9]. Neonates receiving cumulative benzyl alcohol exposures of 100 to 240 mg/kg/day through multiple preserved flush solutions and re-constituted medications developed a syndrome of severe metabolic acidosis with an elevated anion gap, gasping respirations, progressive central nervous system depression, renal failure, thrombocytopenia, hepatic dysfunction, cardiovascular collapse, and death.

The pathophysiology was subsequently characterized as a consequence of the developmental immaturity of neonatal hepatic enzyme systems. Adult metabolism of benzyl alcohol proceeds efficiently through oxidation to benzoic acid and conjugation with glycine to form hippuric acid for renal excretion. In premature neonates, the capacity for glycine conjugation of benzoic acid is limited, leading to accumulation of both benzyl alcohol and benzoic acid to toxic concentrations with repeated dosing [10, 11].

The FDA responded with an advisory recommending the discontinuation of benzyl alcohol-preserved solutions in neonatal patients. This advisory was subsequently incorporated into the labeling of all benzyl alcohol-containing parenteral preparations, including Bacteriostatic Water for Injection, as a contraindication in neonates. The event remains one of the most cited examples of excipient toxicity in a vulnerable population and has shaped regulatory requirements for excipient safety evaluation in pediatric drug development [9, 12].

3.4 Current regulatory and commercial status

Bacteriostatic Water for Injection is manufactured by multiple FDA-registered facilities. The principal branded product is manufactured by Hospira, Inc. (a Pfizer subsidiary) and distributed in 30 mL multi-dose flip-top vials (NDC 0409-3977). Multiple generic manufacturers produce equivalent products under their own NDC listings. The preparation is listed as an essential pharmaceutical product in hospital formularies and is stocked in essentially all hospital pharmacies, compounding pharmacies, and clinical research facilities in the United States.

The product has experienced intermittent supply shortages, most recently in 2019 through 2021, driven by manufacturing capacity constraints, quality-related production interruptions, and increased demand from the compounding pharmacy sector. These shortages have prompted attention to alternative sourcing strategies and to the qualification of non-branded manufacturers [13].

4. Molecular Pharmacology

The molecular pharmacology of Bacteriostatic Water for Injection is the pharmacology of its sole active excipient, benzyl alcohol. The water component has no pharmacological activity beyond its role as a solvent.

4.1 Antimicrobial mechanism of benzyl alcohol

Benzyl alcohol exerts its antimicrobial activity through multiple complementary mechanisms at the bacterial cell level. The primary mechanism is disruption of the bacterial cell membrane phospholipid bilayer. As an amphipathic molecule with a hydrophobic aromatic ring and a hydrophilic hydroxyl group, benzyl alcohol partitions into the lipid bilayer of bacterial cell membranes, increasing membrane fluidity and permeability. This disruption compromises the electrochemical gradient across the membrane, interferes with membrane-associated transport processes (including efflux pumps), and causes leakage of intracellular contents [6, 14].

A secondary mechanism involves interference with bacterial cellular metabolism. Benzyl alcohol disrupts protein synthesis and enzymatic processes at concentrations achieved within the 0.9 percent formulation. The combined membrane and metabolic effects inhibit bacterial cell division without necessarily causing immediate cell death, producing the bacteriostatic (growth-inhibiting) rather than bactericidal (killing) activity that defines the preparation [6, 15].

4.2 Antimicrobial spectrum and efficacy

At 0.9 percent concentration, benzyl alcohol provides effective bacteriostatic activity against common environmental contaminants relevant to multi-dose vial use:

- *Staphylococcus aureus* (Gram-positive coccus): growth inhibition maintained for at least 28 days after vial puncture
- *Pseudomonas aeruginosa* (Gram-negative rod): growth inhibition maintained for at least 28 days, though *Pseudomonas* species are among the more resistant organisms at the 0.9 percent concentration
- *Escherichia coli* (Gram-negative rod): effective growth inhibition

- *Candida albicans* (yeast): moderate inhibition; benzyl alcohol has greater antimicrobial activity against Gram-negative bacteria compared to Gram-positive bacteria or fungi [6, 14]
- *Aspergillus brasiliensis* (mold): limited activity; the preparation does not provide robust antifungal protection

The spectrum is adequate for the intended use (prevention of microbial proliferation in a vial maintained under aseptic technique and refrigerated storage) but is not sufficient for sterilization or for rescue of a grossly contaminated solution. The preparation depends on initial sterility at manufacture and on proper aseptic technique during use [1, 6].

4.3 Interaction with protein and peptide solutes

A pharmacologically important property of benzyl alcohol that is distinct from its antimicrobial activity is its interaction with protein and peptide drug substances during reconstitution and storage. Benzyl alcohol has been shown to interact with the hydrophobic regions of proteins, promoting partial unfolding of tertiary structure and favoring the population of aggregation-competent intermediate conformational states [16, 17].

Published studies have demonstrated benzyl alcohol-induced aggregation of multiple protein therapeutics, including recombinant human growth hormone (rhGH), recombinant human interferon gamma, interleukin-1 receptor antagonist (anakinra), recombinant human granulocyte colony-stimulating factor (filgrastim), and interferon alpha-2a [16, 17, 18, 19]. The aggregation is concentration-dependent: higher benzyl alcohol concentrations produce greater destabilization of protein tertiary structure and more rapid aggregate formation. At the standard 0.9 percent concentration, the effect is modest for most small peptides (fewer than approximately 50 amino acids) but can be significant for larger proteins, particularly at elevated temperatures or over extended storage periods [16, 20].

The practical implication for reconstitution and handling is that the drug product labeling must specify whether Bacteriostatic Water for Injection is an acceptable diluent. For some protein therapeutics, the manufacturer specifies Sterile Water for Injection (without preservative) as the only acceptable diluent, precisely to avoid benzyl alcohol-induced aggregation. For small peptides, growth factors,

and most small-molecule drugs, the 0.9 percent benzyl alcohol concentration is compatible and the multi-dose convenience outweighs the marginal stability consideration [20, 21].

4.4 pH effects

The pH of Bacteriostatic Water for Injection (4.5 to 7.0, typical 5.7) can influence the stability and solubility of reconstituted drug substances. The mildly acidic default pH is a consequence of the equilibrium between dissolved carbon dioxide and the water, combined with the absence of buffering agents. For drug substances that require specific pH ranges for stability or solubility, the drug product formulation typically includes buffering agents in the lyophilized cake or in a separate diluent specification [1, 5].

5. Pharmacokinetics

The pharmacokinetics of Bacteriostatic Water for Injection are the pharmacokinetics of benzyl alcohol, as the water component distributes, equilibrates, and is eliminated as part of total body water without discrete pharmacokinetic phases.

5.1 Absorption

Benzyl alcohol is rapidly absorbed from subcutaneous and intramuscular injection sites. Following parenteral administration as a component of a reconstituted drug product, the benzyl alcohol dose delivered per injection is determined by the volume administered and the 0.9 percent concentration. For a typical 1 mL subcutaneous injection, the delivered benzyl alcohol dose is 9 mg. For a 2 mL intramuscular injection, the dose is 18 mg. These doses are well within the range that adult hepatic metabolism handles efficiently [10, 22].

5.2 Distribution

Benzyl alcohol distributes rapidly into tissues following parenteral administration. The compound is lipophilic and partitions into cell membranes and lipid-rich tissues. Plasma protein binding has not been extensively characterized for benzyl alcohol at the low concentrations achieved following administration of Bacteriostatic Water for Injection, but the rapid metabolism limits systemic exposure duration [10, 23].

5.3 Metabolism

The metabolism of benzyl alcohol in adult humans proceeds through a well-characterized three-step hepatic oxidation and conjugation pathway [10, 22, 23]:

Step 1: Oxidation to benzaldehyde. Alcohol dehydrogenase (ADH) catalyzes the oxidation of benzyl alcohol to benzaldehyde. This reaction is rapid and constitutes the initial biotransformation.

Step 2: Oxidation to benzoic acid. Aldehyde dehydrogenase (ALDH) catalyzes the further oxidation of benzaldehyde to benzoic acid. This reaction is also rapid, and benzaldehyde does not accumulate to significant concentrations under normal metabolic conditions.

Step 3: Glycine conjugation to hippuric acid. Benzoic acid is conjugated with the amino acid glycine in a reaction catalyzed by glycine N-acyltransferase (also known as acyl-CoA:glycine N-acyltransferase) in hepatic mitochondria. The product, hippuric acid (N-benzoylglycine), is a water-soluble conjugate that is efficiently excreted by the kidneys. This conjugation step is the rate-limiting step of the pathway, and its capacity determines the maximum rate of benzyl alcohol clearance [10, 22].

The efficiency of this pathway in adults has been quantified: within 6 hours of oral administration of 1.5 g of benzyl alcohol, adult subjects excreted 75 to 85 percent of the dose in urine as hippuric acid [22]. The glycine pool is not depleted under normal conditions of benzyl alcohol exposure from Bacteriostatic Water for Injection use, as endogenous glycine synthesis provides ample substrate for conjugation [22, 24].

5.4 Neonatal metabolism

The critical pharmacokinetic distinction between adults and neonates is the immaturity of the glycine conjugation pathway in premature infants. Neonatal hepatic glycine N-acyltransferase activity is substantially reduced relative to adult levels, and the capacity for benzoic acid conjugation is limited. When neonates receive repeated doses of benzyl alcohol-containing preparations (as occurred with preserved flush solutions in the 1982 gasping syndrome cases), benzoic acid accumulates, producing severe metabolic acidosis. The accumulation of both benzyl alcohol itself and its metabolite benzoic acid contributes to the toxicity syndrome [9, 10, 11].

The LD50 of benzyl alcohol in neonatal mice is substantially lower than in adult mice (approximately 0.56 g/kg in neonates versus 1.6 g/kg in adults), confirming the developmental pharmacokinetic vulnerability [11, 25].

5.5 Elimination

Renal excretion of hippuric acid is the principal elimination pathway for benzyl alcohol in adults. Less than 1 percent of administered benzyl alcohol is excreted unchanged in urine. The elimination is therefore predominantly metabolic, with the kidney serving as the excretory organ for the conjugated metabolite. Renal impairment may reduce hippuric acid clearance, but the clinical significance at the low benzyl alcohol doses delivered by Bacteriostatic Water for Injection is minimal in adult patients with moderate renal impairment [10, 22].

5.6 Routes of administration

Bacteriostatic Water for Injection is not itself administered as a therapeutic agent. It is used as a vehicle for reconstitution and dilution, and the route of administration is determined by the drug product being reconstituted. The preparation is suitable for intravenous, intramuscular, and subcutaneous routes as specified by the drug product labeling [1, 2]. Direct intravenous administration of Bacteriostatic Water for Injection without a dissolved drug is contraindicated because the solution is hypotonic and would cause hemolysis of red blood cells.

6. Preclinical Pharmacology

6.1 Antimicrobial effectiveness studies

The antimicrobial effectiveness of benzyl alcohol at 0.9 percent concentration has been validated through USP Chapter 51 antimicrobial effectiveness testing, which is the regulatory standard for demonstrating preservative adequacy in multi-dose parenteral preparations. The test protocol challenges the formulation with defined inoculum concentrations of five reference organisms (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans*, and *Aspergillus brasiliensis*) and monitors microbial recovery at defined time points over 28 days [6, 26].

At 0.9 percent benzyl alcohol, the formulation meets USP Category 1 criteria for parenteral preparations: no increase in bacterial counts from the initial inoculum at 7 days, with no recovery of viable organisms by 28 days for bacterial challenge organisms. Fungal challenge organisms show stasis or modest reduction. The test is performed under conditions simulating multi-dose vial use, including storage at controlled room temperature (20 to 25 degrees Celsius) [6, 26].

6.2 Benzyl alcohol toxicology in animal models

Acute toxicity studies of benzyl alcohol in rodent models have established LD50 values of approximately 1.2 to 1.6 g/kg in adult mice (intraperitoneal and intravenous routes) and approximately 0.56 g/kg in neonatal mice, confirming the age-dependent toxicity that underlies the neonatal contraindication [11, 25]. Acute toxicity in adult animals is characterized by central nervous system depression, respiratory depression, and cardiovascular collapse at high doses.

Subchronic toxicity studies of benzyl alcohol at concentrations relevant to pharmaceutical preservative use (0.9 to 2 percent in parenteral formulations administered daily for 28 days) have not produced significant organ toxicity in adult animal models. Hepatic enzyme induction is minimal at these concentrations. Renal histopathology is unremarkable. Local injection site reactions (mild tissue irritation, transient erythema) have been observed at higher benzyl alcohol concentrations (greater than 2 percent) but are minimal at 0.9 percent [25, 27].

6.3 Reproductive and developmental toxicology

Benzyl alcohol has not demonstrated teratogenicity in standard reproductive toxicology studies in rats and rabbits at doses substantially exceeding those delivered by Bacteriostatic Water for Injection. However, the neonatal toxicity signal (gasping syndrome) constitutes a developmental safety concern that applies to the postnatal period rather than to embryonic or fetal development. The FDA labeling accordingly contraindicates use in neonates rather than in pregnant women, though the general recommendation is to avoid unnecessary exposure to benzyl alcohol-containing preparations during pregnancy when preservative-free alternatives are available [9, 12, 27].

6.4 Genotoxicity and carcinogenicity

Benzyl alcohol has been evaluated in standard genotoxicity assays (Ames test, in vitro chromosomal aberration, in vivo micronucleus) and has produced negative results across the battery, indicating no mutagenic or clastogenic potential at relevant concentrations. Long-term carcinogenicity studies have not been conducted specifically for benzyl alcohol at the 0.9 percent concentration used in Bacteriostatic Water for Injection, but the compound has been in continuous pharmaceutical use for over 60 years without signal of carcinogenic activity in human populations [25, 27].

7. Clinical Evidence Base

7.1 Scope of clinical evidence

Bacteriostatic Water for Injection is a pharmaceutical vehicle, not a therapeutic agent, and accordingly has not been the subject of efficacy-oriented clinical trials. The clinical evidence base pertains to the safety of the benzyl alcohol preservative component at the concentrations and cumulative doses encountered in clinical use, and to the functional performance of the preparation as a reconstitution vehicle for specific drug products.

7.2 Safety in adult populations

The safety of benzyl alcohol at 0.9 percent concentration in multi-dose parenteral preparations in adult patients is supported by more than six decades of post-marketing experience across thousands of drug products and billions of administered doses. The cumulative safety record supports the conclusion that benzyl alcohol at this concentration does not produce clinically significant systemic toxicity in adults with normal hepatic and renal function. The maximum recommended daily dose of benzyl alcohol from all parenteral sources is generally cited as 5 mL/kg (equivalent to 45 mg/kg of benzyl alcohol from a 0.9 percent solution), a threshold that is rarely approached in clinical practice [12, 22, 28].

7.3 Safety in pediatric populations (excluding neonates)

In pediatric patients beyond the neonatal period (generally defined as older than 28 days of life for term infants), benzyl alcohol at 0.9 percent concentration is used with caution but is not absolutely contraindicated. The European Medicines Agency has published guidance recommending minimization of benzyl alcohol exposure in pediatric patients, with particular attention to cumulative daily doses from multiple preserved preparations. A threshold of 90 mg/kg/day has been identified as the level above which central nervous system toxicity risk increases in young infants [12, 28, 29].

7.4 The gasping syndrome: clinical characterization

The gasping syndrome, first reported by Gershanik et al. in 1982, was characterized in a series of 10 premature neonates (birth weight 1.0 to 2.5 kg) who developed an acute toxicity syndrome while receiving benzyl alcohol-preserved flush solutions in neonatal intensive care units [9]. The clinical features included:

- Gasping respirations (the pathognomonic sign, occurring in all affected neonates)
- Severe metabolic acidosis with elevated anion gap (reflecting accumulation of benzoic acid)
- Progressive encephalopathy with central nervous system depression
- Intraventricular hemorrhage
- Renal failure with oliguria
- Thrombocytopenia
- Hepatic dysfunction with elevated transaminases
- Cardiovascular collapse and bradycardia
- Skin breakdown

Estimated cumulative benzyl alcohol exposures in affected neonates ranged from 99 to 234 mg/kg/day. Mortality was high. Following the Gershanik report and the FDA advisory, the incidence of the gasping syndrome declined sharply as neonatal units transitioned to preservative-free flush solutions and reconstitution vehicles [9, 10].

7.5 Injection site tolerability

Local injection site tolerability of Bacteriostatic Water for Injection is generally good. The 0.9 percent benzyl alcohol concentration produces mild local anesthetic activity at the injection site, which some patients report as reduced injection pain compared to preservative-free Sterile Water for Injection. This local anesthetic effect of benzyl alcohol has been documented in controlled studies comparing preserved and unpreserved diluents for subcutaneous and intramuscular injections of peptide hormones and growth hormone preparations [30, 31].

8. Sourcing and Quality Verification

8.1 Pharmaceutical-grade sourcing

The highest quality source of Bacteriostatic Water for Injection is an FDA-registered manufacturer producing under cGMP conditions with a current Drug Establishment Registration. The principal branded product is Hospira (Pfizer) Bacteriostatic Water for Injection, USP, supplied in 30 mL multi-dose flip-top polypropylene vials (NDC 0409-3977-03, typically distributed in trays of 25 vials). Multiple generic manufacturers (Fresenius Kabi, B. Braun, Mylan, and others) produce equivalent USP-grade products [1, 2, 13].

Investigators and compounding pharmacies should prioritize sourcing from FDA-registered manufacturers with:

- Current Drug Establishment Registration with FDA
- USP monograph compliance documented in the Certificate of Analysis
- Bacterial endotoxin testing results (less than 0.5 EU/mL)
- Sterility test results per USP Chapter 71
- Benzyl alcohol assay results (0.85 to 0.95 percent w/v, target 0.9 percent)
- pH measurement (4.5 to 7.0)
- Particulate matter testing per USP Chapter 788

8.2 Research-grade and compounding-grade sourcing

Bacteriostatic Water for Injection is also available from research chemical and compounding supply vendors at varying quality levels. Research-grade products from established suppliers (e.g., those marketed for peptide reconstitution) may or may not meet full USP monograph specifications. Investigators should exercise particular caution regarding:

- Endotoxin testing: products marketed as "bacteriostatic water" without explicit endotoxin testing documentation may contain pyrogen levels above the USP limit, which is a significant concern for intravenous or high-volume parenteral use

- Benzyl alcohol concentration: some research-grade products use concentrations other than 0.9 percent (0.9 percent is the USP standard; products at 1.1 percent or higher may increase the risk of protein aggregation and injection site irritation)
- Sterility assurance: products that have not undergone validated terminal sterilization or aseptic fill under cGMP conditions may not be sterile at the point of use
- Container-closure integrity: substandard vial closures may fail to maintain sterility over the labeled 28-day multi-dose use period [4, 13]

8.3 Quality verification on receipt

On receipt of any lot of Bacteriostatic Water for Injection, the following verification steps are appropriate for research and compounding applications:

- Visual inspection for particulate matter, discoloration, or turbidity (the product should be a clear, colorless solution)
- Confirmation of intact container-closure seal (no evidence of prior puncture or seal compromise)
- Review of Certificate of Analysis for benzyl alcohol content, pH, endotoxin, and sterility
- For high-criticality applications (human clinical research, compounding for injection), independent third-party testing for endotoxin and sterility is appropriate
- Verification that the product is within its labeled expiration date and has been stored under appropriate conditions (controlled room temperature, protected from freezing) [1, 4]

9. Reconstitution and Handling

9.1 General reconstitution procedure

The reconstitution of lyophilized drug products with Bacteriostatic Water for Injection follows standard aseptic technique:

1. Remove the flip-top cap from the Bacteriostatic Water for Injection vial and swab the rubber stopper with a 70 percent isopropyl alcohol wipe. Allow to dry.
2. Using a sterile syringe and needle, withdraw the volume of Bacteriostatic Water for Injection specified by the drug product labeling.
3. Swab the rubber stopper of the lyophilized drug product vial with 70 percent isopropyl alcohol. Allow to dry.
4. Inject the Bacteriostatic Water for Injection into the drug product vial, directing the stream against the vial wall to minimize foaming (particularly important for protein and peptide products).
5. Gently swirl (do not shake) the vial until the lyophilized cake is fully dissolved. Shaking can cause protein denaturation and aggregation, particularly for larger proteins and peptide hormones.
6. Inspect the reconstituted solution for clarity, particulate matter, and discoloration. Do not use if particulate matter or discoloration is observed.
7. Record the date and time of reconstitution on the vial label [2, 4].

9.2 Storage of reconstituted solutions

Most reconstituted peptide and protein preparations in Bacteriostatic Water for Injection should be stored under refrigerated conditions (2 to 8 degrees Celsius). The 28-day multi-dose use period begins at the time of first vial puncture of the Bacteriostatic Water for Injection source vial, and the reconstituted drug product has its own beyond-use date as specified by the drug product labeling or by USP Chapter 797 (for compounded sterile preparations) [1, 2, 4].

General storage guidelines for reconstituted solutions:

- Refrigerated storage (2 to 8 degrees Celsius) for the duration of the use period
- Protection from light is recommended for light-sensitive drug substances
- Do not freeze unless the drug product labeling specifically permits freezing of the reconstituted solution
- The 28-day multi-dose use window applies to the Bacteriostatic Water for Injection source vial; the reconstituted drug product may have a shorter or longer beyond-use date depending on the specific drug substance stability profile
- Discard any remaining reconstituted solution after the labeled beyond-use date [2, 4]

9.3 Reconstitution volumes and concentrations

The volume of Bacteriostatic Water for Injection used for reconstitution is determined by the drug product labeling and by the desired final concentration. For research peptides without specific manufacturer guidance, common reconstitution practices include:

- Small peptides (molecular weight less than 5,000 Da): reconstitution to concentrations of 1 to 10 mg/mL is generally well tolerated, with the benzyl alcohol preservative providing adequate stability and bacteriostasis
- Larger peptides and small proteins (molecular weight 5,000 to 50,000 Da): reconstitution to manufacturer-specified concentrations is recommended; higher concentrations may increase the risk of benzyl alcohol-mediated aggregation
- Large proteins (molecular weight greater than 50,000 Da): the drug product labeling should specify whether Bacteriostatic Water for Injection or preservative-free Sterile Water for Injection is the appropriate diluent [4, 20, 21]

9.4 Compatibility considerations

Bacteriostatic Water for Injection is compatible with the majority of small-molecule drugs and small peptides. Specific incompatibilities have been documented for:

- Certain high-molecular-weight proteins that are sensitive to benzyl alcohol-mediated aggregation (see Section 4.3)
- Drug substances that are unstable at the unbuffered pH of 4.5 to 7.0

- Drug substances that require isotonic diluents (Bacteriostatic Water for Injection is hypotonic; Bacteriostatic Sodium Chloride for Injection may be substituted where isotonicity is required)
- Drug substances with specific diluent requirements documented in the approved labeling [1, 2, 20]

10. Stack Interactions and Combinations

The interaction profile of Bacteriostatic Water for Injection pertains to the benzyl alcohol preservative component and its interactions with co-administered drug substances, excipients, and biological matrices.

10.1 Peptide and protein stability interactions

As detailed in Section 4.3, benzyl alcohol at 0.9 percent can promote protein unfolding and aggregation through hydrophobic interactions with protein surfaces. This interaction is relevant when Bacteriostatic Water for Injection is used to reconstitute multi-dose protein preparations. The effect is concentration-dependent and temperature-dependent: refrigerated storage (2 to 8 degrees Celsius) substantially reduces the aggregation rate compared to room temperature storage. For most small peptides commonly encountered in research applications (growth hormone releasing peptides, melanocortin analogs, gonadotropin releasing hormone analogs, and similar peptides with molecular weights below 5,000 Da), the 0.9 percent benzyl alcohol concentration does not produce clinically significant aggregation over the 28-day use period under refrigerated conditions [16, 20, 21].

10.2 Drug substance chemical interactions

Benzyl alcohol can undergo slow oxidation to benzaldehyde in the presence of dissolved oxygen or oxidizing drug substances. Benzaldehyde is a reactive electrophile that can form Schiff base adducts with primary amine groups on drug molecules, peptides, and proteins. Under normal storage conditions (sealed vial, refrigerated, protected from light), this oxidation is minimal and does not produce measurable degradation of the drug substance over the 28-day use period. For drug substances with particularly reactive primary amine groups or for extended storage beyond 28 days, the potential for benzaldehyde-mediated degradation should be evaluated [14, 20].

10.3 Preservative interactions in multi-component formulations

When Bacteriostatic Water for Injection is used to reconstitute drug products that already contain preservatives (such as m-cresol or phenol in insulin or growth hormone formulations), the total preservative load in the final solution increases. The combined antimicrobial effect is additive, but the combined protein-destabilizing effect may also be additive or synergistic. The drug product labeling specifies whether Bacteriostatic Water for Injection is appropriate for products that already contain preservatives, and this guidance should be followed [20, 21].

10.4 Syringe and elastomer interactions

Benzyl alcohol can interact with certain rubber and elastomeric materials used in syringe plungers and vial closures. Specifically, benzyl alcohol can be absorbed into natural rubber components, potentially reducing the effective benzyl alcohol concentration in the solution over time. Modern pharmaceutical vial closures use butyl rubber or synthetic elastomers that have lower absorption of benzyl alcohol. Investigators using non-pharmaceutical-grade syringes or vial components should be aware of this potential interaction [2, 14].

10.5 Combination with other diluents

Bacteriostatic Water for Injection may be combined with other diluents in the same formulation (for example, further diluted with Normal Saline for intravenous infusion). In such combinations, the final benzyl alcohol concentration is reduced proportionally, and the bacteriostatic efficacy may be diminished below the threshold required for multi-dose use. The drug product labeling specifies the acceptable diluent and administration instructions for each specific drug product [1, 2].

11. Adverse Events and Safety Signal

11.1 Adverse events attributable to benzyl alcohol in adults

At the 0.9 percent concentration in Bacteriostatic Water for Injection, adverse events attributable to the benzyl alcohol preservative in adult patients are minimal and principally local:

- Injection site pain: mild stinging or burning at the injection site is reported by a minority of patients. Paradoxically, the local anesthetic properties of benzyl alcohol may reduce injection pain in many patients compared to preservative-free diluents [30, 31]
- Injection site irritation: mild erythema or induration at subcutaneous injection sites is uncommon at 0.9 percent benzyl alcohol and is generally clinically insignificant
- Systemic adverse events: at the benzyl alcohol doses delivered by typical injection volumes (9 to 45 mg per injection for 1 to 5 mL volumes), systemic adverse events are not expected in adults with normal hepatic function. Central nervous system depression, respiratory depression, and cardiovascular effects are dose-dependent toxicities that occur at benzyl alcohol exposures orders of magnitude above those delivered by Bacteriostatic Water for Injection [10, 22, 28]

11.2 Neonatal toxicity (gasping syndrome)

The gasping syndrome is the sole serious adverse event signal associated with Bacteriostatic Water for Injection. As detailed in Sections 3.3 and 7.4, this syndrome is specific to premature neonates with immature benzyl alcohol metabolism and occurs at cumulative daily benzyl alcohol exposures of 100 mg/kg/day or greater. The syndrome is characterized by gasping respirations, metabolic acidosis, encephalopathy, intraventricular hemorrhage, renal failure, and cardiovascular collapse. Mortality is high. The contraindication in neonates is absolute, and the use of preservative-free Sterile Water for Injection is required for all neonatal parenteral applications [9, 10, 12].

11.3 Pediatric caution

In pediatric patients beyond the neonatal period, benzyl alcohol at 0.9 percent concentration should be used with awareness of the cumulative daily dose from all preserved parenteral preparations. The European Medicines Agency guidance recommends calculating the total daily benzyl alcohol exposure in mg/kg and exercising caution above 90 mg/kg/day [12, 28, 29].

11.4 Hypersensitivity

True allergic hypersensitivity to benzyl alcohol is rare but has been reported. Patients with known benzyl alcohol allergy should not receive Bacteriostatic Water for Injection, and preservative-free alternatives should be used. Contact dermatitis to benzyl alcohol has been reported in occupational and cosmetic exposures; parenteral hypersensitivity (anaphylaxis, urticaria) is exceptionally rare [27, 28].

11.5 Intrathecal and epidural contraindication

Bacteriostatic Water for Injection is contraindicated for intrathecal (spinal) and epidural administration. Benzyl alcohol is neurotoxic when applied directly to neural tissue at the concentrations achieved by preservative-containing solutions. Case reports of paraplegia and other severe neurological injury following inadvertent intrathecal administration of benzyl alcohol-containing solutions have been documented. Preservative-free Sterile Water for Injection or Preservative-free Normal Saline must be used for all intrathecal and epidural applications [12, 28, 32].

12. Comparative Assessment

This section presents a structured comparative assessment of five alternative parenteral vehicles against Bacteriostatic Water for Injection, evaluated against five competency standards: novelty of formulation approach, antimicrobial effectiveness, practical utility (multi-dose convenience, stability support, ease of use), side-effect profile (local and systemic), and overall validation (regulatory status, clinical track record, pharmacopeial recognition). The five comparators were selected as the principal alternative aqueous vehicles encountered in pharmaceutical, compounding, and research applications.

12.1 Sterile Water for Injection, USP (SWFI)

Composition: Water for Injection without preservative, packaged in single-dose containers.

Novelty: None. Sterile Water for Injection is the simplest and oldest parenteral vehicle in the pharmacopeial system.

Antimicrobial effectiveness: None. The absence of preservative means that any microbial contamination introduced during vial puncture can proliferate without inhibition. Single-use designation is mandatory; the unused portion must be discarded after initial puncture [1, 3].

Practical utility: Limited by single-dose restriction. For drug products requiring multiple doses from a single reconstituted vial, SWFI is inappropriate unless the entire volume is used within a single dosing event. For single-dose applications, SWFI avoids the benzyl alcohol-related concerns (neonatal contraindication, protein aggregation potential) and is the simplest vehicle available [1, 3].

Side-effect profile: No preservative-related adverse events. Hypotonic; direct intravenous administration without dissolved drug causes hemolysis. No neonatal contraindication [1].

Overall validation: Fully validated. USP monograph, FDA oversight, universal availability. The pharmacopeial reference vehicle for parenteral applications [1, 3].

Comparison to Bacteriostatic Water for Injection: SWFI is the preferred vehicle when: (a) only a single dose will be drawn from the reconstituted vial; (b) the patient is a neonate; (c) the drug substance is a protein known to be destabilized by benzyl alcohol; or (d) the route is intrathecal or epidural. Bacteriostatic Water for Injection is preferred when multi-dose access over days to weeks is required and the patient population permits benzyl alcohol exposure.

12.2 Bacteriostatic Sodium Chloride for Injection, USP (BSCI)

Composition: 0.9 percent sodium chloride (normal saline) with 0.9 percent benzyl alcohol preservative.

Novelty: Minimal. Combines the tonicity of normal saline with the bacteriostatic properties of benzyl alcohol; the formulation has been in use for decades.

Antimicrobial effectiveness: Equivalent to Bacteriostatic Water for Injection. The same 0.9 percent benzyl alcohol concentration provides the same bacteriostatic spectrum and duration [1, 2].

Practical utility: Provides isotonicity (308 mOsm/L), which is advantageous for drug substances that require isotonic diluent to prevent injection site pain, hemolysis, or cell damage. The sodium chloride also provides ionic strength that can improve the solubility of some peptides and proteins. The preparation is used when the drug product labeling specifies isotonic reconstitution [1, 2].

Side-effect profile: Same benzyl alcohol-related considerations as Bacteriostatic Water for Injection (neonatal contraindication, rare hypersensitivity, intrathecal contraindication). The sodium chloride component adds no additional systemic risk at the volumes used. Local tolerability is generally superior to hypotonic BWFI for subcutaneous and intramuscular injections [1, 30].

Overall validation: Fully validated. USP monograph, FDA oversight, universal availability [1, 2].

Comparison to Bacteriostatic Water for Injection: BSCI is preferred when: (a) the drug product labeling specifies isotonic diluent; (b) injection site pain from hypotonic solution is a concern; (c) the drug substance requires ionic strength for sol-

ubility. BWFI is preferred when: (a) the drug product labeling specifies non-saline diluent; (b) the sodium chloride would produce an unacceptable final osmolality when combined with the drug substance.

12.3 Normal Saline (0.9% Sodium Chloride for Injection, USP)

Composition: 0.9 percent sodium chloride in Water for Injection, without preservative. Single-dose containers.

Novelty: None. The standard isotonic crystalloid solution.

Antimicrobial effectiveness: None. No preservative; single-use designation is mandatory [1].

Practical utility: Widely available in a range of container sizes (1 mL to 1000 mL). Isotonic. Suitable for dilution of drugs for intravenous infusion. Not suitable for multi-dose reconstitution due to absence of preservative. Compatible with essentially all parenteral drug substances [1, 2].

Side-effect profile: No preservative-related adverse events. Safe for neonatal use. Safe for intrathecal use. Hyperchloremic metabolic acidosis is a concern only with large-volume intravenous infusion, not with the small volumes used for drug reconstitution [1].

Overall validation: Fully validated. USP monograph, universal availability, the most widely used parenteral solution globally [1].

Comparison to Bacteriostatic Water for Injection: Normal Saline is preferred for single-dose applications requiring isotonicity, for neonatal patients, for intrathecal/epidural routes, and for large-volume intravenous dilution. BWFI is preferred for multi-dose applications where isotonicity is not required.

12.4 Sterile Water for Irrigation, USP

Composition: Purified water meeting less stringent standards than Water for Injection; intended for irrigation of body cavities and surgical sites, not for injection.

Novelty: None. A lower-grade pharmaceutical water.

Antimicrobial effectiveness: None. No preservative [1, 5].

Practical utility: Available in large volumes (500 mL to 3000 mL) at lower cost than Water for Injection. Not suitable for parenteral injection due to less stringent endotoxin and particulate matter specifications. Occasionally misidentified or misused as a reconstitution vehicle for injectable drugs, which constitutes a patient safety risk [1, 5].

Side-effect profile: Not applicable for injection use (contraindicated). For its intended irrigation use, the side-effect profile is minimal [1].

Overall validation: USP monograph for irrigation use. Not validated for injection. Inclusion in this comparator panel serves as a cautionary reference: Sterile Water for Irrigation is not interchangeable with Sterile Water for Injection or Bacteriostatic Water for Injection [1, 5].

Comparison to Bacteriostatic Water for Injection: No overlap in indicated use. Sterile Water for Irrigation must not be substituted for Bacteriostatic Water for Injection in any parenteral application.

12.5 Acetic Acid Water (0.6% Acetic Acid in Sterile Water)

Composition: Sterile Water for Injection with 0.6 percent glacial acetic acid, producing a solution of approximately pH 3.0 to 3.5. Not a USP-monographed preparation; used in research peptide reconstitution.

Novelty: Moderate. Addresses the specific solubility requirements of peptides that aggregate or are poorly soluble at neutral pH. Not a preserved formulation; the acidic pH provides some antimicrobial activity but does not meet USP antimicrobial effectiveness criteria for multi-dose use [33].

Antimicrobial effectiveness: Limited. The low pH (3.0 to 3.5) inhibits the growth of many bacteria but does not provide the validated 28-day bacteriostatic protection of 0.9 percent benzyl alcohol. Not suitable for multi-dose protocols extending beyond a few days without refrigerated storage and strict aseptic technique [33].

Practical utility: Specifically useful for peptides that require acidic conditions for solubility (notably certain amyloid-forming peptides and hydrophobic peptides that aggregate at neutral pH). Not appropriate as a general-purpose reconstitution vehicle [33].

Side-effect profile: The low pH can cause injection site pain and tissue irritation. Not suitable for intravenous administration without further dilution and pH adjustment. Not FDA-regulated as a pharmaceutical preparation [33].

Overall validation: Low. No USP monograph. No FDA regulatory oversight. Used in research applications on the basis of empirical peptide solubility data rather than formal pharmaceutical validation [33].

Comparison to Bacteriostatic Water for Injection: Acetic acid water is a specialized research tool for peptides with pH-dependent solubility requirements. BWFI is the standard multi-dose vehicle for the majority of peptide and drug reconstitution applications. The two are not interchangeable; acetic acid water is selected only when the specific peptide is insoluble or unstable at the pH range of BWFI.

12.6 Comparator summary

Bacteriostatic Water for Injection occupies a unique position among parenteral vehicles as the standard preserved hypotonic diluent for multi-dose reconstitution. Its principal advantage over Sterile Water for Injection and Normal Saline is the 28-day multi-dose use period enabled by the benzyl alcohol preservative. Its principal advantage over Bacteriostatic Sodium Chloride for Injection is the absence of sodium chloride, which is important when the drug product formulation does not tolerate added electrolyte or when the labeling specifies non-saline diluent. Its principal limitation is the neonatal and intrathecal contraindication arising from benzyl alcohol toxicity. No single parenteral vehicle is universally appropriate; vehicle selection is determined by the drug product labeling, patient population, route of administration, and single-dose versus multi-dose requirements.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Bacteriostatic Water for Injection is a pharmaceutical vehicle, not an active therapeutic agent. The compound class considerations and safety profile described herein pertain to the benzyl alcohol preservative component. The neonatal contraindication (gasping syn-

drome risk) is absolute and must not be overridden under any circumstances. Investigators should consult USP monograph specifications and drug product labeling for the specific drug being reconstituted before selecting a parenteral vehicle.