

Benzethonium Chloride: The New Age Antimicrobial

Alchem Opens New
Benzethonium Chloride
Production Facility

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Hand Sanitizers 101

With today's increasing concerns about microbes and viruses, personal hygiene is even more critical to ensure better protection. Although there are many hand sanitizers on the market, **it is essential that a hand sanitizer meet four key Food and Drug Administration Topical Antimicrobial Tentative Final Monograph (FDA-TFM)²⁻⁴ criteria to be considered effective^{5, 6}:**

1. The product should be fast-acting or act within 15 seconds.
2. It should have widespread action against various bacteria, viruses and fungi.
3. The effectiveness of the product should improve after repeated use.
4. A kill time study should show that more than 99% of the germs are killed within 15 seconds.

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Types of Hand Sanitizers

There are a number of hand sanitizers on the market with the following active ingredients for germicidal (killing germs) or germistatic (inhibiting germs) action¹:

Quaternary ammonium salts:

- Alkyl benzalkonium chlorides (most commonly used)
- Benzethonium chloride (BEC)
- Cetrimide
- Cetylpyridium chloride

Others:

- Alcohol
- Chlorhexidine
- Chloroxylenol
- Hexachlorophene
- Iodine and iodophors
- Triclosan



Why Benzethonium Chloride USP?

Alchem's benzethonium chloride meets all of the FDA-TFM criteria for hand sanitizers^{8,9}:

- 1. Speed of Action (Fast Acting):** The antimicrobial activity is immediate upon contact with one log reduction within one minute (e.g., the log₁₀ reduction values for *Escherichia coli* were 1.70 + 0.7).
- 2. Spectrum of Action (Broad):** Minimum inhibitory concentrations (MIC) studies demonstrated the widespread antimicrobial activity of the formulation against aerobic and anaerobic gram-positive bacteria, gram-negative bacteria, and yeasts. It is also effective against Herpes simplex virus, Human Immunodeficiency Virus (HIV) and influenza virus.
- 3. Length of Action (Persistence):** The efficacy improved with repeated use (e.g., the log₁₀ reduction values for *Escherichia coli* after five uses were 2.75 + 1.13).
- 4. Kill time study:** Shows 99% or more reduction in bacterial, viral and fungal count in 15 seconds.

Comparison of Speed and Length of Action of Various Active Molecules¹⁰

BEC is effective within 10 seconds of handwash application. A short exposure time of 10 seconds with 0.2% benzethonium chloride (BEC) is effective. On comparing 60% ethyl alcohol handrub, 0.75%, 2%, and 4% chlorhexidine gluconate (CHG), and 1% triclosan, only BEC was found effective after 10 episodes of hand-washing.





Powerful Antimicrobial²⁸

Benzethonium chloride is more effective against gram-positive than gram-negative bacteria.



Fast-Acting

BEC is effective within 10 seconds of application. A short exposure time of 10 seconds with 0.2% BEC is effectual.

A Comparative Analysis of Hand Sanitizers^{11, 12}

The active ingredients in hand sanitizers each have their own advantages and disadvantages:

1. The most widely used **alcohol-based** hand sanitizers cause drying of skin with loss of essential lipids on repeated use. Alcohol is flammable and volatile. Repeated use decreases the antimicrobial action. There is the possibility of intoxication where teens and school children are likely to ingest it. Waterless alcohol hand sanitizers need periodic hand washing, which is liable to poor compliance. The effect of alcohol stays for just 5 seconds before it evaporates from skin. Alcohol-based products can also destroy industrial floor wax, paint, and materials.
2. **Chlorhexidine gluconate** (CHG) can be irritating to eyes, with minimal antimicrobial activity towards mycobacteria, can damage the ear canal if splashed with water, and can cause sensitization.
3. **Iodophors** or iodine-like compounds can irritate the skin, and stain clothes and the skin. They can also cause corrosion to metals, and sensitization has been reported with Iodophors.
4. **Triclosan**, another common active ingredient, has slower antimicrobial activity than alcohol, and a less persistent activity than CHG and iodophors.
5. **Benzethonium chloride** has less acute oral toxicity than Benzalkonium chloride (BKC), the most widely-used quaternary ammonium compound. While several studies have identified allergic reactions to BKC¹³⁻¹⁹, there have been no reported allergic reactions to BEC. Both products have a similar efficacy spectrum in rinse-off products. However, BEC has a longer persistent action than a combination of alcohol, BKC, and CHG²⁰.

Benzethonium Chloride Advantages^{21,22}

- Broad spectrum activity against both gram positive and negative bacteria, fungi and viruses
- Is effective as a topical skin and wound cleaner
- Bactericidal effect may be seen after 6 hours of usage
- Efficacy improves with repeated usage
- Its acute oral toxicity is lower than the most commonly used QAC, benzalkonium chloride
- Stable and not flammable
- Since it is water-based, it can break through dirt

- No drying action on skin like alcohol
- No sensitization reported
- Does not require rinsing before and after application
- No harsh effect on industrial floor wax, paint, and materials

Fewer Disadvantages²³

- Efficacy is formulation-dependent
- Moderate to slight oral toxicity, although safe at dosages of 0.5% in cosmetic skin applications

Efficacy Profile of Benzethonium Chloride

The antimicrobial activity of QACs has been used for preoperative washing of hands by surgeons since 1935²⁴. Like other QACs, BEC is mainly bacteriostatic and fungistatic with germicidal action at high concentrations²⁵. The compound acts by absorbing the germ's cytoplasmic membrane followed by leakage of cytoplasmic constituents of low molecular weight²⁶. The antimicrobial effect is diluted in the presence of organic matter, dirt, and anionic detergents²⁷.

Benzethonium Chloride in Combination With Sugar Alcohols²⁹

In Vitro Studies: In an in vitro study on *Candida albicans* biofilm, three sugar alcohols (erythritol, xylitol and sorbitol) were found to enhance the fungicidal effect of BEC. Further studies may help in improving BEC hand sanitizer formulations by combining sugar alcohols with BEC.

Benzethonium Chloride as a Preservative in Alcohol-Based Hand Sanitizers

Human and In Vitro Studies³⁰: A study was conducted to evaluate an alcohol-based surgical hand disinfectant, consisting of a zinc gel and a preservative system containing a synergistic combination of farnesol and benzethonium chloride (ZBF disinfectant). The results for the ZBF disinfectant exceed the FDA-TFM criteria for immediate, persistent, and sustained activity required for surgical hand disinfectants both in in-vitro and in-vivo models (on hands of human volunteers).

Benzethonium Chloride in Combination with Essential Oils³¹

Benzethonium chloride in combination with essential oils is bactericidal (sustained 3 log¹⁰ reduction in cfu/mL from the initial inoculums) against all strains of methicillin-resistant *Staphylococcus aureus* by 6 hours.

List of Finished Products Containing Benzethonium Chloride Currently on the U.S. Market

- Betco® Clario™ Alcohol Free Foaming Hand Sanitizer³²
- DermaRite'S Hand-E-Foam³³
- Hylamine³⁴
- Kutol³⁵
- Lonzagard³⁶
- Phemerol Chloride³⁷
- SUDS Non-Alcohol Hand Sanitizer³⁸

Combination Products

- Gold Bond Ultimate Hand Sanitizer (Benzethonium Chloride+moisturizers+ vitamins)³⁹
- Monk Hand Sanitizing Wipes (active ingredient BEC; inactive ingredients: Water, Ethanol, Sodium Benzoate, Diazolidinylurea, Glycerin, Propylene Glycol, Potassium Sorbate, Edetate Disodium, Alpha-Tocopherol Acetate, Aloe)⁴⁰
- Ovation Instant Hand Sanitizer (active ingredient BEC; inactive ingredients: water, dimethicone, glycerin, DMDM Hydantoin, isdopropynyl butylcarbamate, fragrance, hydroxyethyl cellulose)⁴¹
- Lonzagard (active ingredient BEC, inactive ingredients: biocides, didecyl dimethyl ammonium chloride, glutaraldehyde, surfactant, complexing agent, corrosion inhibitor, ph regulation, solvents, water deionized)⁴²

Competitive Products

Benzalkonium chlorides

1. MicroArmor Instant Foam Hand Sanitizer ⁴³
2. SafetySmart®⁴⁴

Alcohol-based hand sanitizers

CONTROL COPY
 UNIT ISSUING
 QUALITY CONTROL



PRODUCT SPECIFICATION

UNIT ISSUING: QUALITY CONTROL

PRODUCT BENZETHONIUM CHLORIDE USP		
Document Number: SPEC: 6952/U-Rev.01	EFF. DATE: 25/09/2010 PAGE NO. : 1/1	SUPERSEDES: 6952/U-Rev.00 DATE: 13/08/2010
TEST	REQUIREMENT/ LIMIT	TEST METHOD REFERENCE
DESCRIPTION	White crystals, having a mild odor. Its solution (1 in 100) is slightly alkaline to litmus.	Visual
SOLUBILITY	Soluble (1 gm in 10 to 30ml) in water, in alcohol, and in chloroform, slightly soluble (1gm in 100 to 1000 ml) in ether.	All tests as per STM-6952/U-Rev.01
IDENTIFICATION	A. To 1 ml of a solution (1 in 100) add 2 ml of alcohol, 0.5ml of 2 N nitric acid, and 1 ml of silver nitrate TS: a white precipitate, which is insoluble in 2N nitric acid but soluble in 6N ammonium hydroxide, is formed. B. A solution (1 in 100) forms precipitates with 2N nitric acid and with mercuric chloride TS, both of which dissolve upon the addition of alcohol.	
MELTING RANGE	Between 158° and 163°	
LOSS ON DRYING	NMT 5.0%	
RESIDUE ON IGNITION	NMT 0.1%	
LIMIT OF AMMONIUM COMPOUNDS	To 5 ml of a solution (1 in 50) add 3ml of 1N sodium hydroxide, and heat to boiling: the odor of ammonia is not perceptible.	
ASSAY (on dried basis)	97.0% to 103.0%	
RESIDUAL SOLVENT Ethyl acetate	NMT 5000 ppm	
<i>[Signature]</i> 25/09/10 PREPARED BY	<i>[Signature]</i> 25/09/10 CHECKED BY	<i>[Signature]</i> 25/09/10 APPROVED BY

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