

Product Development Project:

Surgical Irrigation Solution – Benzoyl Peroxide plus Sterile Water USP

Intended to reduce the incidence of intra- and post-surgical *c. acnes* infections which oftentimes requires additional medical intervention and/or revision surgery – ultimately improving clinical outcomes

P. acnes has become increasingly recognized as a cause of infection in orthopedic surgery, especially postarthroplasty.

In shoulder arthroplasty, infection rates for anatomical arthroplasty have been reported to be <4%, but as high as 18% following reverse polarity arthroplasty.

In one study, the most common bacteria identified were *Staphylococcus epidermidis* and *P. acnes*.

In a retrospective review (over 7 years) from Canada, 80 patients were identified who had positive joint cultures after primary shoulder arthroplasty and *P. acnes* was found to be the second most common pathogenic organism in 25% of participants.

A study of PJI after total shoulder arthroplasty (in the last 33 years) found that *Staphylococcus* was the dominant organism, whereas from 2001 to 2008, the incidence of *P. acnes* was found to be almost as high as *Staphylococcus*.

This increasing incidence could be the result of changes in the microbiology of shoulder infections, heightened awareness of the organism, better surveillance, or improved laboratory diagnostic techniques.

Concerning soft tissue shoulder surgery, deep infection after rotator cuff repair can occur in up to 1.9% of cases, with studies finding *P. acnes* to be the most common causative organism.

Evidently, *P. acnes* appears to be a prominent organism in postoperative shoulder infections and is becoming increasingly prevalent.

Name	Irrisept
Active or Key Ingredient	Chlorohexadine gluconate 0.05%
Packaging Configuration	Sterile 450 mL bottle
Intended Use Indication	Surgical Site Infection (SSI) Prophylaxis
Company	Irrimax
Action	The mechanical action of the Irrisept system helps remove bacteria, particulate and debris in wounds without harming underlying tissues. The bottle design allows users to control pressure of the solution through manual bottle compression.
Notes	There is no mention of effectiveness of the CHG against c. acnes during surgery. The mechanical irrigation is what assumes the removal of debris and or pathogens.



Name	Betadine
Active or Key Ingredient	Povidone Iodine 10%
Packaging Configuration	Unsterile 16 oz (473 mL) bottle
Intended Use Indication	Skin prep before surgery diluted with saline to prevent and treat SSIs
Company	Purdue Pharma
Action	The effect of Povidone Iodine in Betadine starts immediately after application on the skin. Betadine begins oxidizing cell constituents. The active ingredient in Betadine iodinate the microbial protein and DNA with a motive to destroy them



Name	Dakin's Solution
Active or Key Ingredient	Sodium Hypochlorite .25%
Packaging Configuration	Unsterile 475 mL bottle
Intended Use Indication	Prevention and Treatment of SSI
Company	Century Pharmaceutical
Action	solvent action on dead cells hastens the separation of dead from living tissue.
Notes	Preparations of Dakin's solution are sometimes unstable and can be stored for only a few days.



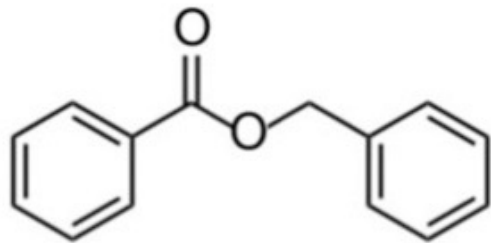
Name	Normal Saline
Active or Key Ingredient	Sodium Chloride 0.9%
Packaging Configuration	1 and 3 liter IV bags
Intended Use Indication	1.SSI Prophylaxis 2. Treatment of SSI
Company	B Braun and others
Action	Mechanical removal (stream of water, pressure controlled by user) washing out and diluting bacteria



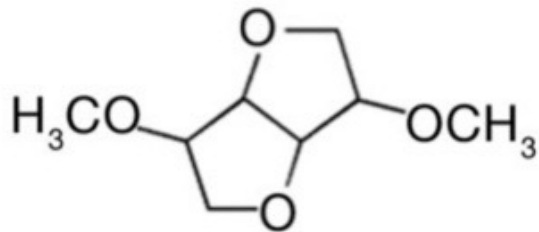
Formulation Work - Consultant

- Formulation Scientist – Neda Irani (Riley)
 - 15+ yrs Pharmaceuticals as a Senior Scientist
 - Product Development
 - Manufacturing
 - Technology Transfer
 - Process Optimization
- Solubility of BPO is poor - must develop and characterize any formulations greater than 0.075%

Formulation Work – Poor Solubility of BPO



Benzyl Benzoate



Dimethyl Isosorbide

“Like Dissolves Like”

	Formula: Clean & Clear brand Persa-Gel 10 ^c	Brevoxyl-4 brand gel ^a	CLENZIderm M.D. brand serum gel ^b
Ingredients	BPO 10% Carbomer Disodium EDTA Hydroxylpropyl Methylcellulose Laureth 4 Sodium Hydroxide Water (<i>aqua</i>)	BPO 4% Cetyl Alcohol Stearyl Alcohol Simethicone Propylene Glycol Alginate Dimethyl Isosorbide Water (<i>aqua</i>) Fragrance (<i>parfum</i>)	BPO 5% Benzyl Benzoate BHT Cyclomethicone Dimethyl Isosorbide Ethoxydiglycol Silica

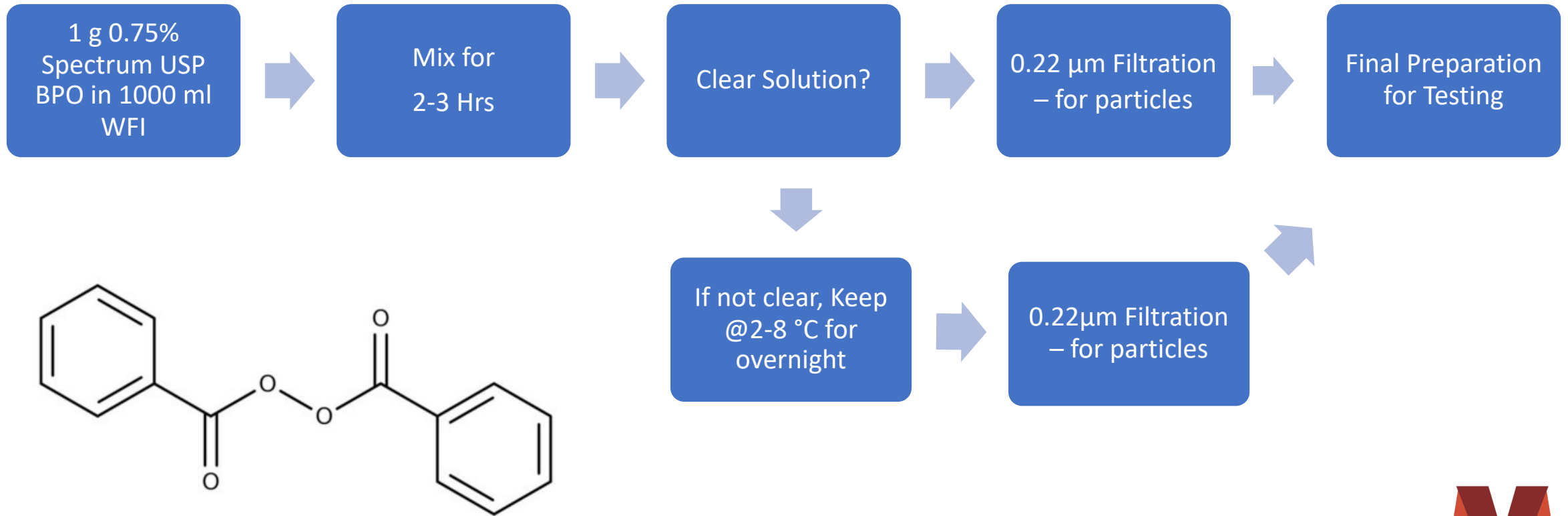
BPO – Mechanism of Action

- The free-radical reaction of benzoyl peroxide can break down the keratin, therefore unblocking the drainage of sebum (comedolytic)
- It can cause nonspecific peroxidation of *C. acnes*, making it bactericidal
- Skin irritation
 - In a 1977 study using a human maximization test, 76% of subjects acquired a contact sensitization to benzoyl peroxide
 - Formulations of 5% and 10% were used

Development Rationale - CutiClense

- Primary Hypothesis
 - OTC Benzoyl Peroxide, 5% and 10% is effective against *c. acnes* when applied topically to the skin
 - Supported by current products in the market and clinical literature
- Primary Research
 - Is aqueous Benzoyl Peroxide 0.075% (BPO) dissolved in USP grade, water for injection (WFI) and filtered for particulates sufficient to neutralize *c. acnes* in vitro?
In vitro – conducted by NAMSA a Contract Research Organization (CRO)
In vivo – human clinical data required (Note: Irrimax Study at Univ of Michigan)
 - Does aqueous Benzoyl Peroxide 0.075% (BPO) dissolved in USP grade, water for injection (WFI) and filtered for particulates cause acute inflammatory reactions or cell disruption when injected directly into muscle tissue?

Mixing Protocol – Test Samples



Quotes from NAMSA - Contact Research Organization (CRO)

- Microbiological Testing - Less Costly, More Ethical
 - Effectiveness against targeted bacteria
 - Mixing/Preparation of Samples – Laminar Flow Hood
- Biocompatibility Testing – Additional Validation of Intended Use
 - Muscle injection
 - Observe Day 1, 3 and 5
 - Review then Approve Final Report