

# 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	<p>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.</p> <p>CHG is different in that it only attacks the cell wall – which then exposes the bacteria to an external harsh environment. Not an oxidizer.</p>
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	Betadine begins is an <b>oxidizing agent</b> , oxidizing by iodinating (destruction of DNA by a strong bonding force) iodine is very reactive, as are peroxides



Why is this not poured directly into a wound?

- CHG does not meet current European specifications for a hand disinfectant. Under the test conditions of the European Standard EN 1499, no significant difference in the efficacy was found between a 4% solution of chlorhexidine digluconate and soap.
- In the U.S., between 2007 and 2009, Hunter Holmes McGuire Veterans Administration Medical Center conducted a cluster-randomized trial and concluded that daily bathing of patients in intensive care units with washcloths saturated with chlorhexidine gluconate reduced the risk of hospital-acquired infections.
- Whether prolonged exposure over many years may have carcinogenic potential is still not clear. The Food and Drug Administration (FDA) in the USA recommendation is to limit the use of a chlorhexidine gluconate mouthwash to a maximum of six months.
- When ingested, CHG is poorly absorbed in the gastrointestinal tract and can cause stomach irritation or nausea. If aspirated into the lungs at high enough concentration, as reported in one case, it can be fatal due to the high risk of acute respiratory distress syndrome.

Name	<b>Dakin's Solution</b>
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	<p>Preparations of Dakin's solution are sometimes unstable and can be stored for only a few days.</p> <p>The antimicrobial effectiveness of sodium hypochlorite is based in its high pH which interferes in the cell membrane integrity with an irreversible enzymatic inhibition, band alterations in cellular metabolism and phospholipid degradation observed in lipidic peroxidation. Cell destruction.</p>



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	<p>Mechanical removal (stream of water, pressure controlled by user) washing out and diluting bacteria</p> <p>Not effective against most bacteria – only as a wash but with applied pressure, it can remove bacteria (or just move them around the wound - if not suctioning)</p>

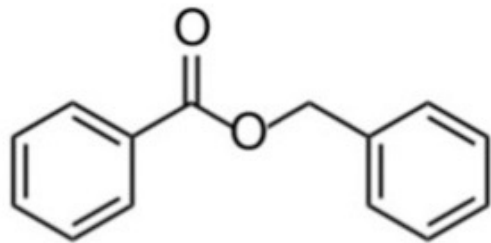


# Formulation Work - Consultant

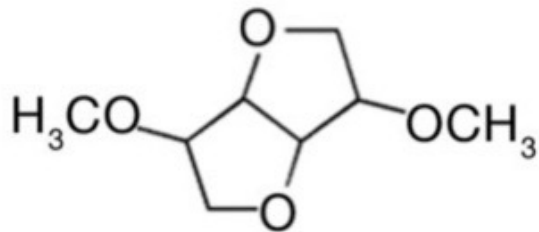
- Formulation Scientist – Neda Irani (Riley)
  - 15+ yrs Pharmaceuticals as a Senior Scientist
  - Product Development
  - Manufacturing
  - Technology Transfer
  - Process Optimization
- Solubility of BPO is poor - must develop and characterize any formulations greater than 0.075%



# Formulation Work – Poor Solubility of BPO



Benzyl Benzoate



Dimethyl Isosorbide

*“Like Dissolves Like”*

## Additional Formulation Requirements

	Formula: Clean & Clear brand Persa-Gel 10 <sup>c</sup>	Brevoxyl-4 brand gel <sup>a</sup>	CLENZIderm M.D. brand serum gel <sup>b</sup>
<b>Ingredients</b>	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

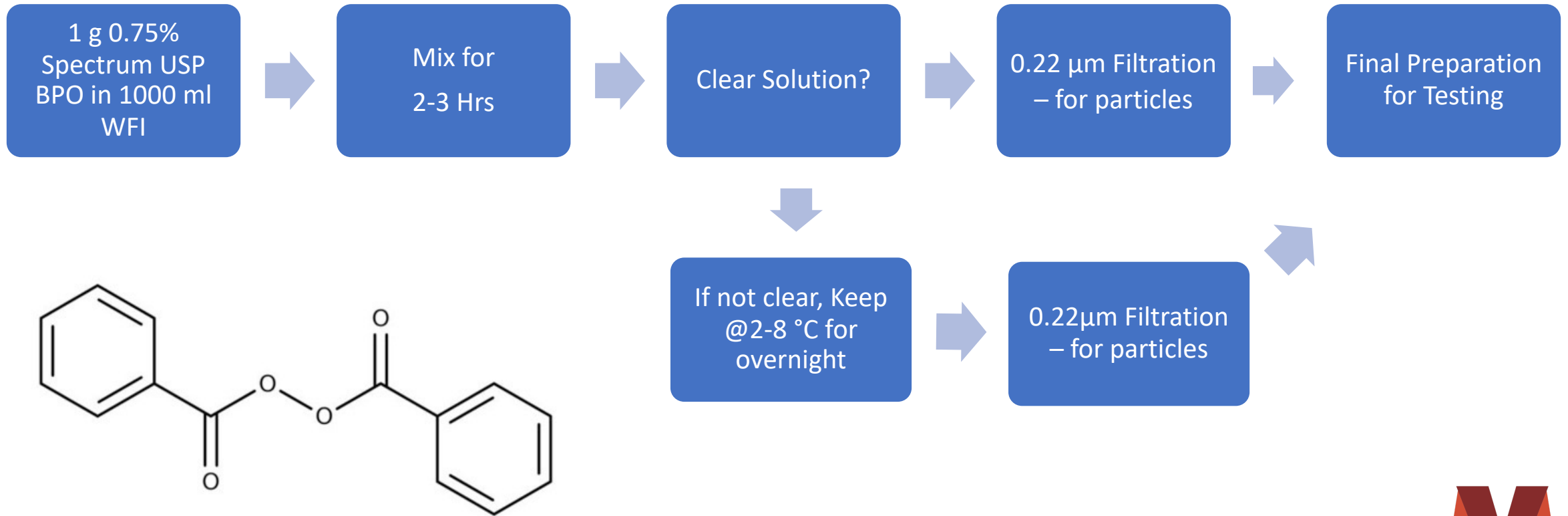
# BPO – Mechanism of Action

- The free-radical reaction of benzoyl peroxide can break down the keratin, therefore unblocking the drainage of sebum (comedolytic)
  - When do you shave the patient? Curious question – release of sebum occurs when?
- 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 - Contract 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 7
  - Review then Approve Final Report