

### Origins of Dakin's Solution

Dakin's Solution was developed in 1914, by the English chemist Henry Drysdale Dakin, and a French surgeon, Alexis Carrel. After their long search for an ideal wound antiseptic, it was used to irrigate wounds and treat infected battlefield wounds, during World War I. This revolution Carrel-Dakin wound treatment saved numerous soldiers' lives and limbs. The Carrel–Dakin treatment consists of the periodic irrigating of an entire wound surface with the Dakin's Solution. Since then, the solution has been used for antiseptic purposes.

### Before Century manufactured Dakin's Solution

Before Century began manufacturing Dakin's Solution, retail and hospital pharmacists around the United States would compound Dakin's Solution on an "as needed" basis. Even today pharmacists without access to manufactured Dakin's Solution must compound the solution themselves. A Dakin's Solution compounded within any hospital pharmacy typically last only up to seven (7) days.

### The stability of Dakin's Solution when compounded

Sodium Hypochlorite Solution, by its nature, deteriorates quickly, especially when it is exposed to light or heat, or when it becomes contaminated with metallic ions. Because of its unstable characteristics, the United States Pharmacopoeia (USP), current revision, states that the shelf life of Sodium Hypochlorite Topical Solution is not more than seven (7) days after the date on which it was compounded.

After the solution has been compounded on-site, it is not possible for a pharmacist or other health care provider or the patient to visually tell whether the Sodium Hypochlorite Topical Solution has deteriorated. The only way to check its potency is by chemical analysis, and most facilities are not willing to perform the analysis required, nor are they equipped to do so.

All of the above resulted in a product that has to be compounded frequently, depending upon the severity of the patient's condition, and used quickly. Obviously, this is not the most effective or efficient method of producing this product. In contrast, when Century manufactures Dakin's Solution, it lasts from 12 to 24 months, depending on the product's concentration. Obviously, this frees up the pharmacist's time and provides the patient with a consistent strength with every batch ordered. Additionally, it helps to ensure that the product is readily available when needed by the patient.

### The stability of Dakin's Solution when made by Century

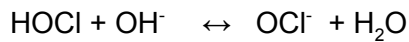
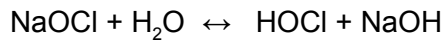
Dakin's products (Sodium Hypochlorite Topical Solutions) manufactured by Century Pharmaceuticals use purified water with low metallic ions; and the products are manufactured under a validated control process, to ensure the uniformity of each batch. Century monitors and tests every single lot of Dakin's multiple times until its expiration

date. This is done to assure the batch maintains its effectiveness throughout its stated expiration date. If a batch shows signs of losing potency, Century can take action before the product actually does lose its potency.

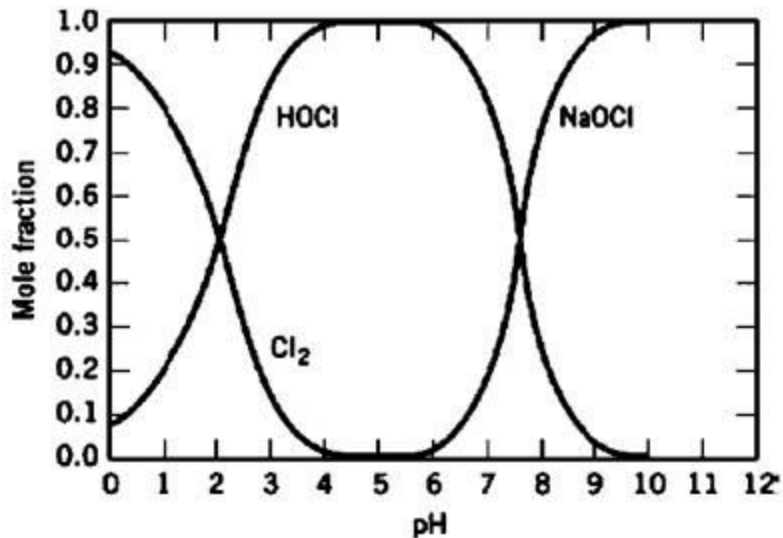
Hospital pharmacists and other health care providers prefer to use Dakin's manufactured by Century because it is more convenient and it offers up to 24 months shelf life, which is a longer shelf life than the solutions compounded on-site. The Century Dakin's products also significantly lower labor costs at the retail or hospital level, helping to keep healthcare costs lower.

### Mechanism of Actions

Sodium hypochlorite (NaOCl) is a sodium salt of hypochlorous acid (HOCl). In solution, sodium hypochlorite dissociates to hypochlorous acid and sodium hydroxide. This chemical equation shows equilibrium sign because the chemical equation can progress to either sodium hypochlorite or hypochlorous acid due to the pH of the solution.



As the pH decreases, the ratio of hypochlorous acid to sodium hypochlorite increases. At pH 1-2 chlorine gas ( $\text{Cl}_2$ ) is the predominant chlorine species, at pH 3-7 hypochlorous acid (HOCl) is predominant, and at pH > 8 sodium hypochlorite (NaOCl) is the major species present as shown in the graph below.



In general, hypochlorous acid is a weak and unstable acid, existing only in solution.

Hypochlorous acid is an unstable strong oxidizing agent because the chlorine molecule is lightly bound and therefore easily to react. Sodium salt of hypochlorous acid or sodium hypochlorite is typically in alkali or base form, which is more stable. In any hypochlorite solution including sodium hypochlorite and hypochlorous acid, the active moiety is the same.

### **Advantages of using Dakin's (Sodium Hypochlorite Topical Solution) products**

#### Antibiotic Drug Resistance

It's well known that infectious diseases caused by antibiotic-resistant bacteria have become an increasingly serious public health problem. Diseases that were formerly curable, such as tuberculosis, gonorrhea, typhoid, and malaria have become resistant or more difficult to treat with antibiotic drugs. Public health experts state that the emergence of these resistant bacteria is attributable to the misuse and overuse of antibiotic drugs.

More and more drug resistant bacteria were isolated from infected wounds. Among these resistant bacteria, the most well-known are MRSA (Methicillin Resistant *Staphylococcus aureus*) and VRE (Vancomycin Resistant *Enterococcus faecalis*). The increasing wound infection caused by resistant microorganisms results in greatly limited choice of antibiotic to be used in wound management.

Dakin's Solution, a broad spectrum antimicrobial, after having been used for over 90 years in various settings, by both patients and healthcare professionals, has not demonstrated any evidence, to the best of our knowledge, showing that its use contributes to antibiotic resistance. Additionally, Dakin's Solution is effective against viruses, yeasts, molds, and bacteria; even bacteria resistant to antibiotics. Dakin's products can help fight the antibiotic resistant skin infections especially MRSA (Methicillin Resistant *Staphylococcus aureus*) infections because these bacteria are not resistant to Dakin's products.

Century hired independent third party laboratories to perform antimicrobial effectiveness tests using USP method of our Di-Dak-Sol (Diluted Dakin's Solution) and WoundClenz, the lowest concentration of Dakin's products, containing sodium hypochlorite solution 0.0125%. The results showed that Di-Dak-Sol (Sodium Hypochlorite 0.0125% Topical Solution) was effective against variety of microorganisms including bacteria, viruses, yeasts, molds, and resistant microorganisms. The resistant microorganisms that were tested include the most famous wound resistant bacteria, namely MRSA (Methicillin Resistant *Staphylococcus aureus*) and VRE (Vancomycin Resistant *Enterococcus faecalis*).

These resistant bacteria, MRSA and VRE, at the initial concentration of  $1.8 \times 10^7$  or higher, were killed after exposure to Di-Dak-Sol or WoundClenz for **only 30 seconds**. The percent reduction or percent kill of MRSA and VRE, the resistant bacteria, were at least **99.99999%** after 30 seconds exposure to Di-Dak-Sol or WoundClenz, which is

Sodium Hypochlorite 0.0125% Topical Solution, the lowest concentration of Dakin's products manufactured by Century Pharmaceuticals. This is the worst case scenario, the higher concentration of our Dakin's products, namely Dakin's Full Strength, Dakin's Half Strength, and Dakin's Quarter Strength are also effective against variety of microorganisms including bacteria, virus, yeast, mold, and resistant microorganisms.

Effectiveness of Di-Dak-Sol and WoundClenz by Century Pharmaceuticals, Inc. (Sodium hypochlorite solution 0.0125%) against microorganisms

<b>Microorganism Tested</b>	<b>% Reduction (or % Kill)</b>
Acinetobacter baumannii 020411-3	99.99999
Aspergillus niger ATCC 16404	99.9999
Bacteroides fragilis ATCC 25285	99.99999
Candida albicans ATCC 10231	99.9999
Clostridium difficile ATCC 9689	99.9
Corynebacterium amycolatum ATCC700206	99.999
Enterobacter aerogenes 022411-2	99.9999
Entrobacter faecium ATCC 19434	99.999999
Erysipelothrix rhusiopathiae ATCC 19414	99.999999
Escherichia coli ATCC 11775	99.999999
Haemophilus influenzae ATCC 49766	99.99999
Klebsiella oxytoca 061611-1	99.999999
Klebsiella pneumonia 071912-3	99.99999
Micrococcus luteus 020610-5	99.999999
MRSA ATCC BAA-38	99.999999
Mycobacteria marinum BAA-535	99.99999
Mycoplasma pneumonia ATCC 29343	99.9999
Propriobacterium acnes ATCC 11827	99.999999
Proteus mirabilis ATCC 14153	99.999999
Pseudomonas aeruginosa ATCC 9027	99.999999
Serratia marcescens ATCC 13477	99.999999
Staphylococcus aureus 080510-7	99.999999
Staphylococcus epidermidis 111611-1	99.99999
Staphylococcus haemolyticus ATCC 29970	99.99999
Streptococcus agalactiae ATCC 12386	99.99999
Streptococcus mutans ATCC 35668	99.999999
Streptococcus pyogenes 031210-7	99.999999
Vibrio vulnificus ATCC 27562	99.9999
VRE ATCC 700221	99.99999

Cost Effectiveness for using in Chronic and Complex Wounds

According to Kalorama Information, Global sales for the chronic and complex wound

market sector were over \$20 billion in 2014. With the growing aging population and people with diabetes, the cost of expenditures for chronic and complex wounds are projected to rise dramatically. The cost of using Dakin's products to treat infected wounds is much lower than most other wound care treatments. Healthcare and wound care professionals continue to recognize the **cost effectiveness** of using Dakin's products to treat infected wounds especially chronic and complex wounds. On December 22, 2013, USA today reported a story entitled "Soldier Blown Apart by War Stages Stirring Comeback. Family, Army doctors witness medical miracle". In one part of the story mentioned persistent fungal infection among wounded soldiers causes multiple amputations and even lives of soldiers. The story continue to mention the successfully used of Dakin's Solution applied directly to the wounds to stop the wound infection after many medications were failed.

### Safety and Efficacy of Sodium Hypochlorite Topical Solutions

Sodium Hypochlorite Solution has a long history and has been widely used for disinfecting purposes, including, but not limited to:

- disinfecting drinking water
- sanitizing household surfaces
- disinfecting food processing equipment
- disinfecting hospital equipment
- sanitizing farm surfaces and equipment
- treating swimming pool water
- treating well water systems
- treating municipal water systems
- treating sewer and waste water systems.

Solutions of sodium hypochlorite are commonly used under a variety of circumstances to ensure microbial cleanliness and international and national standards exist for some usages.

Century hired independent third party laboratories to perform closed patch sensitization, acute eye irritation, acute oral toxicity, acute inhalation toxicity, and primary skin irritation tests for Dakin's Full Strength (Sodium Hypochlorite solution 0.5 %), which is the highest concentration among Dakin's products to show the worst case scenario. The results of the tests are as follows.

- Closed patch sensitization test: Dakin's Full Strength is a non-sensitizer.
- Acute eye irritation test: ocular administration of Dakin's Full Strength produced eye irritation, which cleared within 72 hours.
- Acute oral toxicity test: the LD<sub>50</sub> of Dakin's Full Strength is greater than 5000 mg/kg of body weight.
- Acute inhalation toxicity test: the LD50 of Dakin's Full Strength is greater than 2.1 mg/liter.
- Primary skin irritation test: Dakin's Full Strength is a non-irritant.

Dakin's solution, an antiseptic topical solution containing Sodium Hypochlorite is safe and has been widely used since World War I for antiseptic purposes, including the treatment of traumatic or chronic wounds, burns, skin grafts, pressure ulcers, as well as diabetic leg and foot ulcers.

It's also been used as an antiseptic to prevent infection in pre- and post- operative patients, in dialysis patients, and in endodontic irrigation patients.

The safety and efficacy of Sodium Hypochlorite Topical Solutions have been recognized among pharmacists, physicians, nurses and wound care professionals.

#### References:

- Gregg Zoroya. Soldier Blown Apart by War Stages Stirring Comeback. Family, Army doctors witness medical miracle. USA Today for The Indianapolis Star, Monday December 23, 2013.
- Alice Barsoumian, Carlos J. Sanchez, Katrin Mende, Charla C. Tully, Miriam L. Beckius, Kevin S. Akers, Joseph C. Wenke, Clinton K. Murray. In Vitro Toxicity and Activity of Dakin's Solution, Mafenide Acetate, and Amphotericin B on Filamentous Fungi and Human Cells. J Orthop Trauma, 2013; 27 (8): 428–436.
- Louis Lewandowski, Richard Purcell, Mark Fleming, Wade T. Gordon. The Use of Dilute Dakin's Solution for the Treatment of Angioinvasive Fungal Infection in the Combat Wounded: A Case Series. Military Medicine, 2013; 178 (4): e503-e507.
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