DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Ludovico Giavotto
Alcavis International
8322 Helgerman Court
Gaithersburg, Maryland 20877

APR 24 2009

Donald E. Segal
Alston & Bird LLP
The Atlantic Building
950 F Street N.W.
Washington, D.C. 20004-1404

Re: Docket No. FDA-1975-N-0012
(Legacy Docket No. 1975N-183H)
Comments No. CP13, LET33, LET34, LET41, LET42, SUP9, MM7, C92, FDA-N-1975-0012-0015, FDA-1975 N-0012-0016, and FDA-1975-N-0012-0017
and
Docket No. FDA-1975- N- 0013
(Legacy Docket No. 1975N-183F)
Comments No. CP4, MM1, C22, FDA-1975-N-0013-0020, FDA-1975-N-0013-0021, and FDA-1975-N-0013-0022

Dear Mr. Giavotto and Mr. Segal:

This letter responds to your citizen petitions (CP) 1975N-183F dated January 29, 1999 (CP4) and 1975N-183 H dated February 22, 2002 (CP13). We previously responded to CP13 on November 14, 2002 (LET33). This letter also responds to your correspondence about CP 13 that were dated December 20, 2002 (LET34), June 5, 2003 (LET41), June 17, 2003 (LET42), July 1, 2003 (SUP9), February 10, 2004 (FDA-1975-N-0012-0016), March 15, 2004 (MM7), July 15, 2005 (FDA-1975-0012-0017), October 4, 2006 (C92), and February 6, 2009 (FDA-1975-0012-0015) and to matching correspondence concerning CP 4 dated February 10, 2004 (FDA-1975-N-0013-0021), March 15, 2004 (MM1), July 15, 2005 (FDA-1975-N-0013-0022), October 4, 2006 (C22), and February 6, 2009 (FDA-1975-N-0013-0020).

Your submission of CP13 requested that the U.S. Food and Drug Administration (FDA, or the Agency):

- Reopen the administrative record for the Tentative Final Monograph (TFM) for over-the-counter (OTC) Healthcare Antiseptic Drug Products (59 *Federal Register* (Fed. Reg.)

FDA-1975-N-0012

LDN

31402 (June 17, 1994)) to consider data regarding the safety and effectiveness of sodium hypochlorite (NaOCl) 0.10 to 0.50% as an OTC patient preoperative skin preparation for access site preparation; and

- Amend the TFM based on these data.

Your submission of CP4 requested that FDA:

- Reopen the administrative record for the TFM for OTC First Aid Antiseptic Drug Products (56 Fed. Reg. 33644 (July 22, 1991)) to consider data regarding the safety and effectiveness of NaOCl 0.05 to 0.50% as an OTC first aid antiseptic; and

- Amend the TFM based on these data.

We have reviewed your petitions and the information contained in the correspondence related to CP 13. We have evaluated CP 13 and CP 4 together because they rely on much the same data, and we are providing a complete response to both petitions at this time. For the reasons described in detail in this response, we deny your requests that FDA reopen the records and amend the Tentative Final Monographs for OTC Healthcare Antiseptic Drug Products and OTC First Aid Antiseptic Drug Products to include NaOCl at the concentrations and for the uses specified in your petitions.

I. Executive Summary

Your petitions request that NaOCl at your specified concentrations be included in the Tentative Final Monographs for OTC Healthcare Antiseptic Drug Products and OTC First Aid Antiseptic Drug Products. The basis for your requests and the Agency's responses to each request are summarized in this section and are discussed in further detail in the following sections, including the identification of additional data requirements.

A. Eligibility for the OTC Drug Review (the Review)

You have provided literature references documenting the historical use of NaOCl and evidence of the commercial marketing of the following NaOCl products: (1) Hychlorite, (2) various NaOCl solutions, (3) Dakin's Solution, and (4) Zonite (including a product label copyrighted 1917). Your position is that the long historical use of NaOCl for wound treatment, burns, and other medical indications, as well as the recent and current use of the ingredient as a topical antiseptic, demonstrate that NaOCl has been used to a material time and a material extent and is not a new drug.

The Agency has determined that you have not provided sufficient data to support the eligibility of NaOCl at the concentrations and for the uses specified in your petitions.

- You have not provided labeling that demonstrates marketing prior to 1972 of a NaOCl product at your specified concentrations (0.1 to 0.50%) for use as a preoperative skin preparation.

- There is labeling of a product marketed prior to 1972 that may support eligibility of a first aid use claim for products with an NaOCl concentration of 0.18 to 0.20% (which is not the entire range of requested concentrations, *i.e.*, 0.05 to 0.50%). Notwithstanding, this labeling does not establish monograph eligibility for this limited concentration because data are lacking that establish the pH or the specific qualitative and quantitative formulations of such a product that may have been commercially marketed in the United States prior to 1972. This prevents us from adequately defining and evaluating for eligibility purposes the previously-marketed product because the effectiveness and stability of NaOCl formulations varies with the pH-dependent equilibrium established between hypochlorous acid (HOCl) and hypochlorite ions (OCl^-), *i.e.*, the active antimicrobial moieties.

B. General Recognition of Effectiveness Determination

The petitions present as evidence of NaOCl's antiseptic effectiveness data from: (1) clinical studies, (2) in vivo clinical simulation studies, and (3) a variety of in vitro microbiological assays. Your position is that these data support that NaOCl has a long history of demonstrated effectiveness as an antiseptic and disinfectant.

The Agency has determined that these data are not sufficient to demonstrate the effectiveness of NaOCl for use either as a patient preoperative skin preparation or as a first aid antiseptic.

C. General Recognition of Safety Determination

The petitions present published and unpublished data from a number of preclinical and clinical studies that you believe have repeatedly demonstrated the ingredient's safety. In particular, you state that the toxicity and carcinogenicity of NaOCl has been extensively examined. Based on the available data and the lack of toxicology or carcinogenicity concerns that have been identified during the long history of use, you believe that NaOCl should be considered noncarcinogenic, nonmutagenic, and essentially not toxic for the proposed uses at the proposed concentrations. You also believe that NaOCl has been shown to be essentially nonirritating, and not an inhibitor of wound healing or a skin sensitizer.

We do not have sufficient information at this time to characterize the active ingredient or the appropriate pH range for NaOCl solutions. Therefore, we are unable to determine the relevance of the submitted safety data (preclinical and clinical) to your requests. An evaluation of the safety of the ingredient would be premature at the present time.

D. Previous Communications on CP13 and CP 4

FDA responded to CP 13 in a letter dated November 14, 2002 (LET33). In our response, we stated that you did not present information showing a marketing history of NaOCl as a patient preoperative skin preparation in the United States. We recommended that you use the Time and Extent Application (TEA) process to establish the eligibility of this ingredient for evaluation under FDA's OTC Drug Review. FDA did not evaluate CP 4 in the response letter dated November 14, 2002.

In your subsequent submissions dated December 20, 2002 (LET34), June 5, 2003 (LET41), June 17, 2003 (LET42), July 1, 2003 (SUP9), February 10, 2004 (FDA-1975-N-0012-0016 and FDA-1975-N-0013-0021), March 15, 2004 (MM7and MM1), July 15, 2005 (FDA-1975-0012-0017 and FDA-1975-0013-0022), and October 4, 2006 (C92 and C22), you disagreed with our determination regarding CP 13, requested that we reconsider our position, and made the following arguments:

- FDA's determination is premature and a TEA would be inappropriate.
- CP 13 provides the necessary evidence of the ingredient's historic use as a general antiseptic and disinfectant since World War I.
- Historically, several other products were used on the skin prior to surgery and for numerous other topical uses. These products were often called a skin antiseptic.
- While NaOCl has not been labeled specifically as a patient preoperative skin preparation, it has been labeled generally for use on wounds and more specifically for surgery.
- Historical documents provided in CP 13 support the premise that use for surgery entails cleansing of both wounds and skin.
- The current definitions for these types of products are arbitrary and have changed over time. The term "patient preoperative skin preparation" does not adequately describe the various antiseptic uses that are meant to be included in the definition, and must be interpreted broadly. For example, the preamble to the 1994 Healthcare Antiseptic Drug Products TFM expressly provides that "patient preoperative skin preparation" includes the antisepsis of the skin prior to the insertion of catheters (59 Fed. Reg. at 31425).
- The proposed indications for use in the relevant monographs are intended to be broad and to capture, in today's terminology, safe and effective ingredients. These may have been offered for sale in different terminology during previous generations. For example, the First Aid monograph is not restricted to considering

only those ingredients that were promoted, word-for-word, for use as "antiseptic treatment for minor cuts, scrapes, and burns," as the current indication is specified.

II. FDA Evaluation of Eligibility for OTC Drug Review

A. Requirements for the Demonstration of Eligibility for the OTC Drug Review

1. General Requirements

The OTC drug monograph system was established to evaluate the safety and effectiveness of all OTC drug products marketed in the United States on or before May 11, 1972 that were not covered by a new drug application (NDA), and all OTC drug products covered by "safety" NDAs that were marketed in the United States before enactment of the 1962 drug amendments to the Federal Food, Drug and Cosmetic Act (the Act), 21 U.S.C. § 201, *et seq*. *See* Procedures for Classification of OTC Drugs, 37 Fed. Reg. 9464 (May 11, 1972). Since the inception of the OTC Drug Review, FDA has maintained that an OTC drug product is covered by that review as long as its indication, route of administration, and dosage level existed in the OTC drug marketplace on or before May 11, 1972[1].

To determine eligibility for the OTC Drug Review, FDA must have actual product labeling or a facsimile of labeling that documents the conditions of marketing of a product prior to May 1972. 21 CFR § 330.10(a)(2). Conditions include active ingredient, dosage form, dosage strength, route of administration, and specific OTC use of the product. 21 CFR 330.14(a). These are the same criteria used to establish that OTC drugs initially marketed in the United States *after* the Review began or without any U.S. marketing experience meet the "material extent" or "material time" provisions of the Act's "new drug" definition (21 U.S.C. § 201, section 201(p)(2)) and are eligible for the Review. *See* 21 CFR § 330.14(c)(3). Accordingly, literature or other materials that reference or describe the general use of NaOCl without detailing a specific product's conditions of OTC marketing are insufficient to demonstrate eligibility for inclusion in the OTC monograph.

FDA also has maintained that *only* those uses described in the labeling for OTC drugs marketed in the United States on or before May 11, 1972 are covered by the OTC Drug Review. For example, FDA responded to a 1984 citizen petition filed by George R. P. Farquhar of Capitol Sanitizing Systems, Inc. (the Farquhar Petition) about inclusion in the monograph of a combination of two quaternary ammonium compounds. While the combination had been in the U.S. OTC drug marketplace before the OTC Drug Review was established for use by food handlers as an antiseptic handwash, it was not considered eligible for the different uses proposed by the petitioner, *e.g.* as an antiseptic handwash for health-care

---

1 37 FR 9464 at 9464, May 11, 1972 - Procedures for Classification of Over-the-Counter Drugs ("OTC drugs *now marketed*)

personnel, an antiseptic preoperative skin preparation, an antiseptic surgical scrub, and for general skin antiseptic use. FDA advised that such a product offered for such uses was a new drug that required NDA approval before it could be legally marketed. FDA's denial of the Farquhar Petition was upheld in *Farquhar v. FDA*, 616 F. Supp. 190, 192 (D.D.C. 1985) (upholding FDA's position that pre-1972 marketing history of an OTC drug product for one use does not make that product eligible for the OTC Drug Review for another use that has no such prior marketing history in this country).

2. Specific Requirements Related to CP 13 and 4.

   a. Scope of the Patient Preoperative Skin Preparation Indication

      The current definition of a patient preoperative skin preparation is "a fast acting, broad spectrum, and persistent antiseptic containing preparation that significantly reduces the number of micro-organisms on intact skin." *See* Tentative Final Monograph for Healthcare Antiseptic Drug Products, 59 Fed. Reg. at 31442. Your assertion that the definition is arbitrary and has changed over time is incorrect. ([2/10/04 letter] at 3.)

      This definition first was developed by the OTC Topical Antimicrobial I Panel and was included in the Panel's recommendations to FDA in 1974. *See* Proposal to Establish a Monograph for OTC Topical Antimicrobial Products, 39 Fed. Reg. 33103, 33114 (Sept. 13, 1974) (defining patient preoperative skin preparation as "[a] safe, fast-acting, broad-spectrum antimicrobial-containing preparation which significantly reduces the number of microorganisms on the intact skin"). The Panel's definition reflects the labeling of antiseptic products that were submitted in response to earlier FDA calls for data published in the *Federal Register* of January 7 and April 4, 1972. *See* Request for Submission of Data on Antibacterial Drug Ingredients, 37 Fed. Reg. 195, 235 (Jan. 7, 1972); Over-the-Counter Antimicrobial Ingredients in Drug Products, 37 Fed. Reg. 6723, 6775 (April 4, 1972). This definition was accepted by the FDA in its 1978 and 1994 proposed rules. *See* Over-the-Counter Drugs Generally Recognized as Safe, Effective and Not Misbranded, 43 Fed. Reg. 1210, 1246 (Jan. 6, 1978); 59 Fed. Reg. at 31442. FDA received no comments objecting to this definition in response to any of these publications. Thus, the definition of a patient preoperative skin preparation has remained essentially the same throughout the OTC Drug Review and is based on products marketed prior to May 1972.

      You also assert that this definition includes wounds. (CP 13 at 7.) While the Panel received submissions for products bearing an indication for antisepsis in deep infected wounds (*e.g.* Docket No. 75N-0183 (topical antimicrobial rulemaking), Mercresin (OTC vol. 020093); *id.*, Zephiran (OTC vol. 020009)),

this use was not included in the Panel's evaluation of antiseptic products. By contrast, the indications identified in the 1994 TFM for patient preoperative skin preparation, which are based on the Panel's definition of a patient preoperative skin preparation, are "for preparation of the skin prior to surgery," "for preparation of the skin prior to an injection," and "helps reduce bacteria that potentially can cause skin infection." *See* 59 Fed. Reg. at 31443. All of these indications involve the use of antiseptic products on intact skin, and cannot be extended to the management and treatment of severe wounds. Claims for the treatment and management of severe wounds are not covered by FDA's OTC Drug Review and have historically been regarded as prescription drug claims. 21 U.S.C. § 503(b)(1).

b. Scope of the First Aid Antiseptic Indication

First Aid Antiseptic is defined in the First Aid TFM as "[a]n antiseptic-containing drug product applied topically to the skin to help prevent infection in minor cuts, scrapes, and burns." 56 Fed. Reg. at 33677. Contrary to your assertion (C92 at 4), FDA's definition does not require narrow word-for-word adherence to the exclusion of uses that historically may have been described in different terminology. As discussed in Section II.B below, we have accepted the uses found in the labeling of a pre-1972 Zonite product that are consistent with the definition of first aid antiseptic and that are not exact word for word representations of the proposed indications for first aid antiseptics to support the eligibility of the Zonite product for the OTC Drug Review. Thus, the Agency does not interpret this as narrowly as you contend.

c. Characterization of pH of NaOCl Solutions

Due to the chemical nature of the NaOCl, you also must provide information characterizing the pH and the specific qualitative and quantitative formulations of any pre-1972 products referenced by the petition to establish the eligibility of NaOCl for the OTC Drug Review

According to information provided in your petitions, NaOCl in solution affords sodium hydroxide (NaOH) and hypochlorous acid (HOCl) as shown by the following equation:

$$NaOCl + H_2O \leftrightarrow NaOH + HOCl$$

Hypochlorous acid then dissociates to hydrogen ions (H^+) and hypochlorite ions (OCl^-):

$$HOCl \leftrightarrow H^+ + OCl^-$$

Both HOCl and OCl^- are sources for elemental chlorine, to which the antiseptic

activity of NaOCl is attributed. The relative amount of the species HOCl and OCl^- can vary with the pH-dependent equilibrium established between HOCl and OCl^-.

Of the two species, undissociated HOCl is considered the more effective antiseptic. Thus, the effectiveness of the product may vary depending on the amount of HOCl and OCl^- present in the solution. As a consequence, in order to adequately evaluate the ingredients being considered for inclusion in the monograph, we must know the pH of the solutions and other formulation specifics of the products marketed prior to 1972.

In addition to information on pH and other formulation specifics of pre-1972 NaOCl products, it will be necessary to define a pH range that will assure a safe and effective product. The petitions state that Alcavis has determined that an optimal balance between stability and antiseptic effectiveness is achieved at a pH between 10.0 and 10.7 for the undiluted 1.1% NaOCl solution and that the pH is slightly lower after dilution. It is not clear that the pHs cited in the petition are within the range of pHs of the NaOCl products marketed prior to 1972. Additionally, the petition did not provide any of the data demonstrating that the optimal pH range for effectiveness is between 10.0 and 10.7. This information is needed to precisely define the nature of NaOCl solution to be considered for inclusion in an OTC drug monograph.

B. Labeling Information Considered in the Eligibility Determinations for CP 13 and CP 4.

To support the eligibility of NaOCl for the OTC Drug Review for both petitions, you cited evidence of the commercial marketing of the following NaOCl products: (1) Hychlorite, (2) NaOCl solutions, (3) Dakin's Solution, and (4) Zonite. Labeling was provided for one product (Zonite). The Zonite labeling, provided as Exhibit 5 of your October 4, 2006 letter (C92 and C22), includes a copyright date of 1917 and describes the product as "a powerful antiseptic, germ destroyer, disinfectant and deodorant," and "non-poisonous as indicated for the profession and home." The labeling goes on to state that the product is "a concentrated and stabilized form of Carrel-Dakin solution NaOCl." The label does not, however, include specific indications, directions for use, or information on the product formulation as required. It therefore does not suffice as evidence of the commercial marketing of Zonite for use as either a patient preoperative skin preparation or first aid antiseptic.

During our consideration of your petitions, we discovered what may be a previously marketed package of Zonite. (Attached hereto as Exhibit A.) The product's immediate container label and carton labeling include statements about the product's intended uses that are comparable to those included in an advertisement for Zonite from the 1945-1946 Redbook, provided as Attachment 4 of your March 15, 2004 letter (MM7 and MM1). The similarity of the language in this label to the advertisement suggests that it is not unreasonable to believe that this label may date from the 1940's.

The label states that the product is intended for use as a:

- **Gargle** for "raw" or irritated throat
- **Mouth wash** antiseptic deodorant
- **Nasal spray** for use at the first sign of head colds
- **Feminine Hygiene**—germicidal and deodorizing douche solution
- **Germicidal Wash**—hands, feet, etc.,
- **"Athlete's Foot" Symptoms**
- **First Aid Treatment**—kills germs. Wet dressing for surface wounds
- **Cuts, Burns, Skin Abrasions**, externally caused pimples
- **Poison Ivy, Minor Insect Bites, Sunburn**
- **Chafing**—comforting to baby's skin
- **Rectal Applications**—soothes and help healing irritated parts

The carton labeling describes the product as a:

> "personal antiseptic, powerful germicide, feminine hygiene deodorant," and that it is an "electrolytically prepared, mildly alkaline solution containing sodium hypochlorite with sodium hydroxide and sodium chloride in certain carefully controlled proportions," and that "[e]qual parts of Zonite and water will yield a stable solution whose chlorine concentration is the same as Dakin's solution – for use in the irrigation treatment of wounds. Clinical experience has shown that a 1:5 dilution of Zonite is sufficient for most surgical uses."

This label does not support the eligibility of NaOCl for use in the preparation of the skin prior to a surgical procedure or injection (*i.e.*, patient preoperative skin preparation use). The product's labeled claim for use in "the irrigation treatment of wounds" is not comparable to OTC antiseptic use for these purposes. The claims for wound irrigation referenced in the historical literature also are not covered by FDA's OTC Drug Review. These uses require the supervision of a licensed practitioner, and historically have been regarded as prescription drug claims. *See* 21 U.S.C. § 503(b) (1). Further, the labeling statement "clinical experience has shown that a 1:5 dilution of Zonite is sufficient for most surgical uses" is not sufficient to establish the product's use as a patient preoperative skin preparation, given that the ingredient's only documented use for surgery is as an adjunct to the surgical treatment of serious wounds and infections. *See* Table 1, below. We conclude, therefore, that the 1940's Zonite label does not demonstrate the marketing of Zonite for uses comparable to patient preoperative skin preparation.

In contrast, many of the claims made on the 1940's Zonite product label are consistent with the use of the product as a first aid antiseptic and may support the inclusion of NaOCl in the OTC Drug Review for first aid use at the Zonite use concentration. We must next determine, however, whether the concentration of sodium hypochlorite in the 1940's Zonite product is within the specific concentrations sought in CP 4. While the concentration is not stated on

the Zonite label we reviewed, it is possible to calculate the concentration of NaOCl in the product based on statements found on the label and available information about the concentration of NaOCl in Modified Dakin's solution (diluted Dakin's solution). The product labeling states that "equal parts of Zonite and water will yield a stable solution whose chlorine concentration is the same as Dakin's solution..." As described in the 1926 10th Edition and 1936 11th Edition of the United States Pharmacoepia (Refs 38 and 39 of CP13), Modified Dakin's Solution is to contain 0.43 to 0.48% chlorine equivalent to 0.45 to 0.5% NaOCl. Thus, the concentration of NaOCl in the full strength product, prior to dilution, appears to have been approximately 0.9 to 1.0%. This concentration is above the range requested by the petitions.

When diluted according to the labeled directions, however, the product's use concentration falls within the range of NaOCl concentrations requested by the CP 4. The product's actual use concentration based on the labeled directions to dilute one tablespoon of Zonite to ¼ cup water (1:5 dilution) for indications consistent with first aid antiseptic use appears to have been approximately 0.18 to 0.20 %. We believe, therefore, that the label *may* support the eligibility of the concentration of NaOCl in the 1940's Zonite product: 0.18 to 0.20% NaOCl for the indications covered in the 1991 proposed rule for OTC first aid antiseptics. *See* 56 Fed. Reg. at 33677.[2]

While the foregoing may support eligibility of 0.18-0.20% NaOCl for OTC first aid antiseptic use based on the uses described on this Zonite labeling, there are several additional steps you must take in order to demonstrate eligibility as requested in your petition. First, this Zonite label does not demonstrate the eligibility of the broader range of NaOCl concentrations requested by CP4 (0.05 to 0.5%). Additional information in the form of a product label with similar indications but with a different concentration that falls within the range of concentrations requested by the petition is needed to document eligibility of other NaOCl concentrations. Second, the label does not include specifics of the product's formulation including the pH of the solution and the concentrations of other ingredients listed on the Zonite label (sodium hydroxide and sodium chloride), which are necessary to define the product and evaluate eligibility for any concentration sought. *See* Section II.A.2.c. above.

C. Medical Literature Considered in the Eligibility Determinations for CP 13 and CP4.

Your submissions included literature (Refs. 2-10, 21-23, and 26-47 of CP13, and Attachments 3 and 4 of MM7) documenting the history of the use of NaOCl, which is summarized in Table 1, below. The literature references do not fully characterize any individual NaOCl product marketed prior to May 1972, and therefore are insufficient to support eligibility for either CP request.

---

2 Concluding that labeling may be sufficient to demonstrate eligibility for one historical indication but not another is consistent with FDA's response to the Farquhar Petition that the demonstration of one historical use does not suffice to demonstrate eligibility for all other historical uses. *See Farquar*, 616 F. Supp. at 192.

Table 1--Historical Use of NaOCl
(Refs. 2-10, 21-23, and 26-47)

Use	NaOCl Use Concentration
treatment of infected wounds	Dakin's Solution (0.45 to 0.50% NaOCl)
wound debridement	Milton's solution (1% NaOCl)
Stage III and IV decubitus ulcers	Dakin's Solution (0.45 to 0.50% NaOCl)
wound irrigation	Dakin's Solution (0.45 to 0.50% NaOCl)
treatment of burns	Milton's solution (1% NaOCl)
germicide for the treatment of wounds	Dakin's Solution (0.45 to 0.50% NaOCl)
[1]Surgery—where Dakin's solution is indicated: bone suppurations, chronic ulcers, empyema, abdominal infections, in skin grafting and burns	Hychlorite 4.05% solution Wet dressing--1:200 solution of Hychlorite (0.02% NaOCl)
[1]Laryngology—as a spray, snuff, or gargle in suppurative nasal, throat, and ear conditions; in prurulent sinus disease, and tonsillar disease [1]Opthalmology—in prurulent conjunctivitis [1]Urology—in acute and chronic gonorrhea, vaginitis and cystitis, chancroids, and ulcers	For irrigation--1:2,000 to 1:200 solution of Hychlorite (0.02 to 0.002% NaOCl) For topical use and swabs—full or half strength Hychlorite (4.05 to 2.025% NaOCl)
"antiseptic, germicide, fungicide, deodorant, cleansing, and promotes healing," and states that the product is used for cuts, burns, bruises, poison ivy, minor insect bites, and wet dressing for wounds.	Zonite (0.18 to 0.20% NaOCl) (concentration calculated based on labeling that references Dakin's solution)
[2]topical antiseptic	Dakins (0.5%)

[1] No recommendation for the appropriate concentration for these specific uses are listed in Ref. 40

[2] Reference date after 1972

The historical uses of NaOCl as a healthcare antiseptic documented by the references cited in CP13 are not consistent with the use of a patient preoperative skin preparation as defined in the Healthcare TFM. As a general matter, we do not find that the statements made in the literature are an adequate substitute for the information contained in labeling of pre-1972 products. Even today, the medical literature is replete with off-label uses of approved drug products. These off-label uses are not necessarily consistent with product labeling and marketing.

In particular, the majority of the surgical uses described in the references involve wound debridement and irrigation and the treatment of serious infections. We do not consider these uses comparable to patient preoperative skin preparation. Claims for wound care and treatment are not covered by FDA's OTC Drug Review and have historically been regarded as prescription drug claims. *See* Section B, above. In addition, in your March 15, 2004, letter to Dan Troy, former FDA Chief Counsel, you state that Hychlorite was indicated for (among other things) "surgery." You state that use for surgery entails cleansing of both wounds and skin. Such uses of Hychlorite have not, however, been documented in the product labeling that has been submitted to date.

The concentrations of NaOCl identified in the references do not support the concentration range requested in CP13 for patient preoperative skin preparation (0.10 to 0.5%). (Only Dakin's solution (0.45 to 0.50%) falls within that range and does not cover the full range of concentrations requested. Moreover, this concentration was referenced for use in the treatment of severe wounds and infections, which does not fall under either indication sought in the petitions.)

Finally, the literature cited also does not counter the fact that the NaOCl products have been inadequately characterized. As discussed above, the uses set forth in the literature regarding Zonite as a first aid antiseptic may support eligibility for inclusion in the OTC First Aid Antiseptic TFM. The literature does not provide data that allows the product to be adequately characterized, however, and therefore, does not suffice to meet your burden for demonstrating eligibility. Our detailed comments on the references you submitted in support of your petitions are provided in the table attached hereto as Attachment 1.

D. Summary of FDA Response Regarding Eligibility

1. Eligibility for Evaluation Under the OTC Drug Review for the Indications Included in FDA's Proposed Rule for OTC Patient Preoperative Skin Preparation.

   Although NaOCl has a long history of use that predates FDA's OTC Drug Review, the documentation provided in CP 13 and subsequent submissions is not sufficient to demonstrate the marketing of NaOCl for uses consistent with a patient preoperative skin preparation prior to May 1972. Therefore, we believe that NaOCl at a concentration of 0.10 to 0.50% has not been demonstrated to be eligible for the OTC Drug Review as an OTC antiseptic for patient preoperative skin preparation. The following information is needed to demonstrate the eligibility of 0.10 to 0.50% NaOCl as a patient preoperative skin preparation:

   - Labeling (actual or facsimile) from a product or products marketed prior to May 11, 1972, that includes uses consistent with patient preoperative skin preparation use and that reflects the requested range of concentrations

- Information from standard reference texts published prior to 1972 or from manufacturer's literature that defines the pH and describes the qualitative and quantitative formulations of any products referenced

2. Eligibility for Evaluation under the OTC Drug Review for the Indications Included in FDA's Proposed Rule for OTC First Aid Antiseptic Drug

   Based on labeling obtained by FDA for a NaOCl product (Zonite) that appears to have been marketed prior to May 11, 1972, we believe that NaOCl at the Zonite use concentration (0.18 to 0.20%) may be eligible for evaluation under the OTC Drug Review for the indications included in FDA's Proposed Rule for OTC First Aid Antiseptic Drug Products. *See* 56 Fed. Reg. at 33677. However, additional information documenting the pH and the qualitative and quantitative formulation marketed prior to May 1972 is needed for us to make a final determination about the eligibility of this formulation for this indication in the OTC Drug Review.

   The documentation provided is not sufficient to demonstrate the eligibility of the broader range of concentrations of NaOCl requested by CP4 for first aid use (0.05 to 0.50%). The following information is required to demonstrate the eligibility of 0.05 to 0.50% NaOCl for first aid antiseptic use:

   - Labeling (actual or facsimile) from a product or products marketed prior to May 11, 1972, that includes uses consistent with first aid antiseptic use and whose use concentrations reflects the requested range of concentrations

   - Information from standard reference texts published prior to 1972 or from manufacturer's literature that defines the pH and describes the qualitative and quantitative formulations of any products referenced

III. FDA Evaluation of Effectiveness

As set forth above, you have not demonstrated eligibility for inclusion of the requested drug products in either the Healthcare or First Aid Monographs. Notwithstanding, FDA has evaluated the materials submitted with the petitions and in the recent supplements to those petitions in support of the effectiveness of NaOCl for either indication in the event that eligibility is established in the future. Upon review of these materials, FDA has concluded that the data provided to support the effectiveness of NaOCl as a patient preoperative skin preparation or first aid antiseptic are not adequate.

A. Regulatory Standard for Demonstrating Effectiveness of an OTC Active Ingredient

In 21 CFR 330.10(a)(4)(ii), there is a description of the standards for establishing the general recognition of the effectiveness of an OTC active ingredient. Proof of effectiveness "shall consist of controlled clinical studies" as defined in the NDA

regulations unless this requirement is waived. *See id.* (explicitly incorporating 21 CFR § 314.126(b)). Investigations of the effectiveness of an active ingredient may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking sufficient detail for a scientific evaluation will not be considered.

B. There is Insufficient Evidence to Support Effectiveness of NaOCl for the Patient Preoperative Skin Preparation Indication.

1. Evaluation of in vitro data

CP 13 presents a variety of in vitro data that includes the results of standardized foreign and domestic testing for disinfectants and antiseptics and the results of testing conducted using nonstandard testing. Your February 6, 2009 submission (FDA-1975N-0012-0015) provides the results of a time-kill assay of a product containing 0.05% NaOCl. Our evaluation of the data provided in CP13 and the February 6, 2009 supplement to this petition is that it is not sufficient to adequately characterize the spectrum and kinetics of the antimicrobial activity or define the pH and the qualitative and quantitative formulations of the solutions tested for the following reasons:

- The majority of the testing was conducted using a product formulation without adequate comparison to controls (*e.g.*, a vehicle control) to demonstrate the contribution of NaOCl to the observed antimicrobial activity (Refs. 12, 14, 25, 67, 69, 75, 76, 78-88, 91-100, and FDA-1975-0012-0015).

- The pH of the solutions tested is not provided.

- The testing conditions for the studies vary widely with respect to the concentrations tested, exposure times, challenge organisms, and culture conditions. Because of the varying test conditions and methodologies employed, a comprehensive demonstration of broad spectrum activity and the kinetics of the antimicrobial activity of NaOCl for the range of concentrations requested by the petition has not been established.

- Data were not provided for some clinically relevant organisms, *i.e.*, *Serratia marcescens, Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus haemolyticus, Staphylococcus saprophyticus, Streptococcus pyogenes, Streptococcus pneumoniae, Enterococcus faecalis,* and *Enterococcus faecium.*

- Testing was conducted against few clinical isolates.

- Many of the studies lack sufficient detail about important aspects of the study such as neutralizer use and validation and starting inoculums (Refs 4, 79-86 and 91-97).

- The results of testing using foreign standardized tests (Refs. 79-86) are provided in a foreign language without translation.

Adequate and well-controlled in vitro studies defining the spectrum and kinetics of NaOCl's antimicrobial activity over the requested range of concentrations are needed to support efficacy of the ingredient in the monograph as well as data characterizing the pH of solutions tested. In addition, data would need to be submitted to address the potential for the development of resistance to NaOCl.

2. Evaluation of in vivo data

The current standard for the approval of a patient preoperative skin preparation is a demonstration of effectiveness in a clinical simulation study as described in the 1994 TFM. Alternatively, the demonstration of effectiveness of OTC topical antiseptics ideally would be based on well-designed clinical studies demonstrating a clinically meaningful benefit, *e.g.*, a reduction in post-surgical infection. We begin with consideration of the latter type of study.

The petition provided two clinical outcome studies of the use of NaOCl (Refs. 66 and 102). Neither study involved a use relevant to patient preoperative skin preparation prior to surgery or patient care. The studies also have a number of other design limitations.

Mian *et al.* studied the use of a NaOCl-containing product (5 to 10% NaOCl) versus 1% silver sulfadiazine in the treatment of 20 patients with second and third degree burns (Ref. 66). The NaOCl product was applied in a compress that was changed every 8 hours and by immersion of the burn area in an isotonic NaOCl solution for approximately 1 hour at 2- to 3-day intervals. Treatment with the silver sulfadiazine product consisted of the application of the cream every 12 hours. Subjects were evaluated for infection every day or even several times a day for general or local signs of infection, pathologic signs, hydroelectric and metabolic homeostasis, clinical course, reepithelization, escharlysis, granulation, attachment of autografts, and microbiological tests. Microbiological data were collected at the burn site and/or that of a suspected lesion by rubbing a swab over a fixed area of about $1 cm^2$ on days 2, 7, 14, and after one month, at 15-day intervals. The investigators reported that there appeared to be a lower incidence of sepsis among the patients treated with NaOCl than among patients treated with silver sulfadiazine.

This study cannot be considered an adequate and well-controlled study supporting effectiveness of NaOCl for the patient preoperative skin preparation indication for a variety of reasons. The study was not blinded or randomized, nor was any statistical analysis of the data performed (Ref. 66). The treatments consisted of two very different treatment methods, compresses and soaking versus the use of a cream. The observed effects may have been confounded by the use of antibiotic therapy for subjects that the investigators described as being at greater risk. Finally, the study was designed to assess the effectiveness of NaOCl for the treatment of burns and is not supportive of patient preoperative skin preparation claims.

The second clinical study you provided also has little relevance to the use of NaOCl as a patient preoperative skin preparation. Carabelli (Ref. 102) compared the effectiveness of a product containing 0.055% sodium hypochlorite to an unidentified mercurial antiseptic for the treatment of vaginal itching of undetermined etiology in 60 non-hospitalized adult women (Ref. 102). After 3 days of treatment (two 2- to 3-minute washings every 12 hours), the investigator reported that vaginal itching, burning, and redness improved in both groups, but that the total score values were significantly lower after treatment with NaOCl (Mann-Whitney U test, $p< 0.001$). Both antiseptics caused an immediate and large reduction in bacterial counts. Subjects treated with the NaOCl product showed five to ten times less *S. epidermidis* and bacillus species and Gram negative rods completely disappeared in 100% of these patients. The relevance of the observed bacterial reductions to the reduction of symptoms was not assessed.

As stated previously, the currently-proposed standard for the demonstration of the effectiveness of patient preoperative skin preparations in the 1994 TFM is a study that simulates, as much as possible, the actual use conditions for these products. Patient preoperative skin preparations are evaluated at two separate anatomical sites for immediate and persistent antimicrobial effects. The skin sites recommended for use in evaluating the effectiveness of these products represent common surgical sites and include both dry and moist skin sites. The TFM describes a suitable dry site as the abdomen and a suitable moist site as the groin. The effectiveness of test formulations is evaluated at 10 minutes and 6 hours after prepping. Efficacy is demonstrated by a reduction of the microbial flora at each site from a predetermined baseline at 10 minutes and 6 hours. At 10 minutes, the required bacterial reduction is 2.0 $\log_{10}$ for the abdomen and a 3.0 $\log_{10}$ for the groin. The microbial flora cannot exceed the statistical mean baseline by the end of the sixth hour post-product use. 59 Fed. Reg. at 21450-31452.[3]

---

3 The validity and the clinical relevance of the proposed surrogate endpoints for the demonstration of the effectiveness of OTC healthcare antiseptics were discussed at the March 23, 2005 meeting of the Nonprescription Drugs Advisory Committee (NDAC). Based in part on the continuing need for these products and the difficulty in establishing effectiveness of these products in a placebo controlled clinical outcome trial, NDAC concluded that continued reliance on the current effectiveness criteria is appropriate until better methods of assessing the effectiveness of healthcare antiseptics can be developed.

The in vivo data you provided are from clinical simulation studies that do not conform to the testing recommendations of the 1994 TFM. As illustrated by the table below, in the majority of the studies cited by the petition, the test formulations containing 0.11% NaOCl do not meet the relevant effectiveness criteria for a patient preoperative skin preparation.

Table 2--Results of Clinical Simulation Studies Submitted in CP 13

Reference	Reductions	
49a. Roveda, S., et al.[1]	**NaOCl 0.11%**	**Povidone-iodine 10%**
Abdomen 10 minutes	1.79	1.20
Abdomen 4 hours	1.43	1.23
Axilla 10 minutes	2.64	0.86
Axilla 4 hours	2.26	0.83
49b Cruz et al.[1]	**NaOCl 0.11%**	**Povidone-iodine 10%**
Abdomen 10 minutes	1.42	1.44
Abdomen 4 hours	1.03	0.87
Axilla 10 minutes	1.69	2.09
Axilla 4 hours	2.37	2.23
101. Jones and Mulberry[2]	**NaOCl 0.11%**	**Povidone-iodine 10%**
Abdomen 10 minutes	99.4% (2.222)	99.9% (3.000)
Abdomen 4 hours	97.8% (1.658)	99.0% (2.000)
Axilla 10 minutes	95.5% (1.347)	92.5% (1.125)
Axilla 4 hours	99.2% (2.097)	91.5% (1.071)
118. Hill Top Biolabs[3]	**NaOCl 0.11%**	**Povidone-iodine 10%**
forearm (volar aspect) 10 minutes	NR	NR
forearm (volar aspect) 30 minutes	NR	NR
forearm (volar aspect) 4 hours	NR	NR
Abdomen 10 minutes	NR	NR
Abdomen 30 minutes	NR	NR
Abdomen 4 hours	NR	NR
119. Hill Top Biolabs[1]	**NaOCl 0.11%**	**Povidone-iodine (Betadine)**
Abdomen 10 minutes	1.1090	3.0653
Abdomen 4 hours	2.1650	1.5141
Axilla 10 minutes	1.2147	1.4950

Table 2--Results of Clinical Simulation Studies Submitted in CP 13		
Reference	**Reductions**	
Axilla 4 hours	1.0601	1.5935
120. Hill Top Biolabs[1,4]	**NaOCl 0.11%**	**No Active Control**
Abdomen 10 minutes (application method A)	2.2977	
Abdomen 10 minutes (application method B)	1.9516	
Groin 10 minutes (application method A)	2.6580	
Groin 10 minutes (application method B)	2.5272	

[1] Log_{10} reductions
[2] Study reports percent bacterial reductions (corresponding log reductions)
[3] Not reported
[4] Purpose of study is to compare two different application methods

Most of the studies use a moist test site that is not identified in the TFM (*i.e.*, axilla) and fail to achieve the specified log reduction for a moist site. While the test failure may be in part related to the site selected, active controls in many of these studies also fail to meet the required effectiveness criteria. This raises questions about the overall validity of the study results. In addition, one of the studies used artificial enhancement of the resident microbial flora by occlusion (Ref. 118). This method of achieving high bacterial counts has not been validated. In addition, the studies used finished product formulations and are not adequately controlled to demonstrate the contribution of NaOCl. Neither the pH nor the quantitative formulations tested are described.

Based on the in vitro and in vivo data submitted, the Agency concludes that the petitions have not demonstrated effectiveness of NaOCl for use as a patient preoperative skin preparation.

C. <u>There Is Insufficient Evidence to Support Effectiveness of NaOCl for the First Aid Antiseptic Indication</u>.

1. Guidelines for the Demonstration of Effectiveness of First Aid Antiseptic Active Ingredients

You cite the proposed in vitro testing procedures in the TFM for OTC first aid antiseptic drug products published in 1991 as the basis for your conclusions about the effectiveness of NaOCl for first aid antiseptic use. This proposed testing, however, is intended for the demonstration of the effectiveness of final formulations of generally recognized safe and effective first aid antiseptic active ingredients and is not adequate to support the general

recognition of the effectiveness of NaOCl for this use. *See* Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for First Aid Antiseptic Drug Products, 56 Fed. Reg. 33644, 33673 (July 22, 1991). Guidelines for the development of data to demonstrate the effectiveness of topical antimicrobial active ingredients (including topical antimicrobials for first aid uses) are included in the 1978 TFM for OTC topical antimicrobial products. *See* OTC Topical Antimicrobial Products Over-the-Counter Drugs Generally Recognized as Safe and Effective and Not Misbranded 43 Fed. Reg. 1210, 1240 (Jan. 6, 1978). The data described by these guidelines are similar to the testing requirements proposed by FDA in its 1994 TFM to support the effectiveness of OTC healthcare antiseptic drug products and include the following:

In vitro data

- Determination of the antimicrobial spectrum
- Determination of the minimal inhibitory concentration (MIC) under standard conditions against standard organisms and a series of recently isolated mesophilic strains, including representative normal flora and cutaneous pathogens
- Determination of the potential for the development of resistance
- Data substantiating antimicrobial action by standard methods

In vivo data

- Determination of the qualitative and quantitative estimation of the reduction of both transient and resident bacteria
- Determination of the ingredient's effect on wound healing
- Determination of the minimal concentration of the ingredient necessary to produce a first aid antiseptic claim

The data provided to support the effectiveness of NaOCl as a first aid antiseptic are the same references cited to support the ingredient's use as a preoperative skin preparation. Many of the criticisms of the data in the context of preoperative skin preparation discussed above therefore are relevant to the evaluation of effectiveness for first aid antiseptic use.

2. Evaluation of In Vitro Data

The data provided are not sufficient to adequately characterize the spectrum and antimicrobial activity or define the pH and the qualitative and quantitative

formulations of the solutions tested for the following reasons:

- The majority of the testing was conducted using a product formulation without adequate comparison to controls (*e.g.*, a vehicle control) to demonstrate the contribution of NaOCl to the observed antimicrobial activity (Refs. 12, 14, 25, 67, 69, 75, 76, 78-88, 91-100, and FDA-1975-N-0013-0020).

- The pH of the solutions tested is not provided.

- The testing conditions for the studies vary widely with respect to the concentrations tested, exposure times, challenge organisms, and culture conditions. Because of the varying test conditions and methodologies employed, a comprehensive demonstration of broad spectrum activity and MICs has not been established.

- The studies employed few clinical isolates

- Many of the studies lack sufficient detail about important aspects of the study such as neutralizer use and validation and starting inoculums (Refs 4, 79-86 and 91-97).

- The results of testing using foreign standardized tests (Refs. 79-86) are provided in a foreign language without translation.

Data from adequate and well-controlled in vitro studies of the type described above for the requested range of concentrations, as well as data characterizing the pH of solutions tested, are needed to support efficacy of the ingredient for OTC first aid antiseptic use. Data addressing the potential for the development of resistance also would be needed.

3. Evaluation of In Vivo Data

CP4 relies on the same clinical outcome studies (Mian *et al.* (Ref. 66) and Carabelli (Ref. 102)) cited in CP13 to support the effectiveness of 0.05 to 0.50% NaOCl for first aid antiseptic use. The deficiencies in these studies described in Section III.B.2. above also preclude reliance on these studies to demonstrate effectiveness for first aid use. For example, the study Mian *et al.* (Ref. 66) cannot be considered adequate and well-controlled because it lacks blinding, randomization, and statistical analysis, and includes the use of a confounding additional treatment. The use of NaOCl for the treatment of vaginal itching studied by Carabelli (Ref. 102) also is not relevant to the use of the ingredient for use as a first aid antiseptic.

Unlike the healthcare antiseptic drug products, there currently is no proposed

standard to assess the in vivo effectiveness of OTC antiseptics for first aid use. This makes it difficult to assess the relevance of the bacterial reductions observed in the cited clinical simulation studies to first aid antiseptic use. Nor were data provided to support the relevance of the bacterial reductions on intact skin observed in the clinical simulation studies to first aid antiseptic use.

4. Effects on Wound Healing

CP4 provides data from a number of in vitro and in vivo studies of the effects of NaOCl on wound healing (Refs. 8, 11, 25, 28, and 66-69). As discussed above, insufficient data has been provided to characterize the active ingredient or the appropriate pH range for NaOCl solutions. In order for FDA to assess the relevance of the findings from these studies to your request, additional data are needed to fully characterize the nature of the ingredient that would be eligible for the OTC Drug Review.

D. Summary: Data from Adequate and Well-Controlled Studies Are Needed to Support the General Recognition of the Effectiveness of NaOCl for OTC Use

1. Demonstration of the Effectiveness for Use as an OTC Patient Preoperative Skin Preparation

The demonstration of the effectiveness of NaOCl for use as an OTC patient preoperative skin preparation will require data from the following:

- Standardized in vitro studies demonstrating the effectiveness of NaOCl against clinically relevant organisms
- Studies characterizing the kinetics of the antimicrobial activity of the ingredient
- Studies characterizing the potential for the development of resistance to NaOCl
- Data from two clinical simulation studies demonstrating the ability of NaOCl to meet the effectiveness criteria for a patient preoperative skin preparation (2.0 $\log_{10}$ on the abdomen, 3.0 $\log_{10}$ on the groin, and counts not exceeding baseline at six hours)

In addition, as discussed above in footnote three, FDA is in the process of reevaluating the testing protocols included in the 1994 TFM for healthcare antiseptic drug products and is refining these protocols based on discussions of NDAC on March 23, 2005. If you plan to pursue efficacy studies as a patient

preoperative skin preparation with this ingredient, you are encouraged to discuss proposed protocols with FDA prior to initiating these studies.

2. Demonstration of the Effectiveness for Use as an OTC First Aid Antiseptic

The foregoing and specific additional data will be needed to support the ingredient's inclusion in the monograph for OTC first aid antiseptics. The 1978 TFM for topical antimicrobial drug products provides general information about the data necessary to upgrade an antiseptic ingredient to monograph status for OTC first aid antiseptic use. *See* 56 Fed. Reg. at 3673; 43 Fed. Reg. at 1242. We also encourage you to obtain more specific input directly from FDA (*e.g.*, by requesting a pre-IND meeting) on the data requirements for the demonstration of the effectiveness of a first aid antiseptic active ingredient.

IV. FDA Evaluation of Safety

As discussed above, because the data submitted are not sufficient to characterize the active ingredient or the appropriate pH range for NaOCl solutions, any conclusions based on the submitted safety data would be preliminary and would not necessarily be applicable to the fully-characterized active ingredient or a finished product formulation. Therefore, a comprehensive evaluation of submitted data will not be provided until data are submitted that allow full characterization of the nature of the ingredient that would be eligible for the OTC Drug Review.

V. The Compendial Standard for NaOCl

To be included in an OTC monograph, an ingredient requires data demonstrating general recognition of safety and effectiveness. In addition, it must be standardized and characterized for quality and purity and have a current United States Pharmacoepia National Formulary (USP-NF) standard. 21 CFR § 330.14 (c) (1) (i). While USP30/NF25 currently includes a standard for a NaOCl topical solution, it is not consistent with the petitions' requests. The current USP standard is a 0.025% solution and the required pH is between 7.8 and 8.2. *See* United States Pharmacopeia 31—National Formulary 26, United States Pharmacopeial Convention, Inc., Rockville, MD, 2008. The standard further states that the solution is stable for only 7 days after compounding. Therefore, an appropriate standard for the NaOCl antiseptic solutions requested by the petitions does not currently exist.

Because the current USP standard identifies the limited stability of NaOCl solutions (*see id.*), this issue must be addressed for NaOCl to be included in an OTC monograph. FDA needs to be able to fully describe the conditions necessary to achieve a stable product in the monograph. Thus, information characterizing the aspects of a product's formulation necessary for stability and data defining the extent of this stability are required to allow NaOCl's inclusion in an OTC drug monograph. If FDA determines that a product

requires prior review of the stability data on a case-by-case basis, this would preclude marketing under the monograph and require the submission of an NDA.

VI. Conclusion

Based on the deficiencies described in this response, your petitions requesting to re-open the administrative records for the TFMs for OTC healthcare and first aid antiseptic drug products and to include NaOCl in certain concentrations in these monographs are denied.

Eligibility:

You have failed to provide information that adequately characterizes the pH or the specific qualitative and quantitative formulations of NaOCl that were marketed prior to 1972 as indicated for preoperative skin preparation. As a consequence, we are unable to determine what formulation of NaOCl may be considered eligible for the OTC Drug Review.

The first aid use claim is possibly eligible at NaOCl concentrations of 0.18 to 0.20%. However, without adequate characterization of the pH and a description of the qualitative and quantitative formulation of the solution, we cannot make a final determination of eligibility for this indication. Nor can we make a determination regarding eligibility for the remaining concentrations sought in CP 4.

To address the deficiencies in both petitions, you will need to provide labeling (actual or facsimile) from NaOCl products marketed prior to 1972 whose concentrations are consistent with the petitions' requested range of concentrations under the conditions of use. You also will need to provide information on the pH and the qualitative and quantitative formulations of these products. See the detailed discussions in Sections II.2.c., II.B. and II.C.

Effectiveness:

You have not provided sufficient information that supports the efficacy of NaOCl for preoperative skin preparation or first aid use, nor have you defined the pH and the qualitative and quantitative formulation of an effective NaOCl product. Data from adequate and well-controlled in vitro and in vivo studies will be needed to support the ingredient's inclusion in the monograph for OTC healthcare or first aid antiseptics.

Safety:

Based on the lack of data characterizing the qualitative and quantitative formulation and the appropriate pH range for NaOCl, a comprehensive evaluation of the safety data included in the petitions has not been conducted.

Stability:

In order for NaOCl to be considered for inclusion in an OTC monograph, it will be necessary to fully describe the conditions necessary to achieve a stable NaOCl solution. If FDA determines that a product requires prior review of the stability data on a case-by-case basis, this would preclude marketing under the monograph and require the submission of an NDA.

Any comments you wish to make on the above information should be identified with the appropriate docket numbers (FDA-1975-N-0012 and FDA-1975-N-0013) and submitted in three copies to each docket to the Division of Docket Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

Sincerely,

Michael A. Chappell
Acting Associate Commissioner for Regulatory Affairs

Attachment 1: FDA Evaluation of References Concerning the Marketing of NaOCl (5 pages)

Exhibit A: Zonite Labeling (4 pages)

Attachment 1—FDA Evaluation of References Concerning the Marketing of NaOCl		
Source	**Reference (CP13)**	**Evaluation**
CP 4, CP13	2. Wangensteen. O. H. et al.	Review article on post-Listerian Antiseptic wound practices. No information relevant to the marketing conditions of a specific NaOCl product. No concentration of NaOCl provided.
CP4, CP13, LET 41	3. Haller, J. S.	Description of the Carrel–Dakin method in the treatment of infected wounds in World War I. No information relevant to the marketing conditions of a specific NaOCl product. No concentration of NaOCl provided.
CP4, CP13, LET 41	4. Dakin, H. D.	Article on the preparation and use of Dakin's solution for wound irrigation. No information relevant to the marketing conditions of a specific NaOCl product. No concentration of NaOCl provided.
CP4, CP13, LET41	5. Malinin, T. I.	Discussion of the value of the Carrel–Dakin method in context of the treatment of infected wounds by intermittent irrigation with Dakin's solution. No information relevant to the marketing conditions of a specific NaOCl product. No concentration of NaOCl provided.
CP4, CP13, LET 41	6. Sheppard, G. H. and Rich, N. M.	General article on wound management that mentions Carrel-Dakin irrigation tubes. No information relevant to the marketing conditions of a specific NaOCl product. No concentration of NaOCl provided.
CP4, CP13, LET41	7. Farrow, S. and Toth, B.	Article on the risks and benefits of Eusol in wound management. No information relevant to the marketing conditions of a specific NaOCl product. No concentration of NaOCl provided.
CP4, CP13	9. Wright, D.	Description of the use of a 1% Milton solution for treatment of deep burn wounds. No information relevant to the marketing conditions of a specific NaOCl product.
CP4, CP 13, LET41	10. Slehetka, F.	Description of the use of Dakin's solution for the treatment of deep ulcers. No information relevant to the marketing conditions of a specific NaOCl product. Concentration of NaOCl cited: 0.45 to 0.50%.
CP4, CP 13, LET41	21. Carrel, A. and Debelly, G.	Description of the use of NaOCl solutions (Dakin's, eau de Javel, and Labarraque's) for the treatment of infected wounds. No information relevant to the marketing conditions of a specific NaOCl product. No concentration of NaOCl provided.

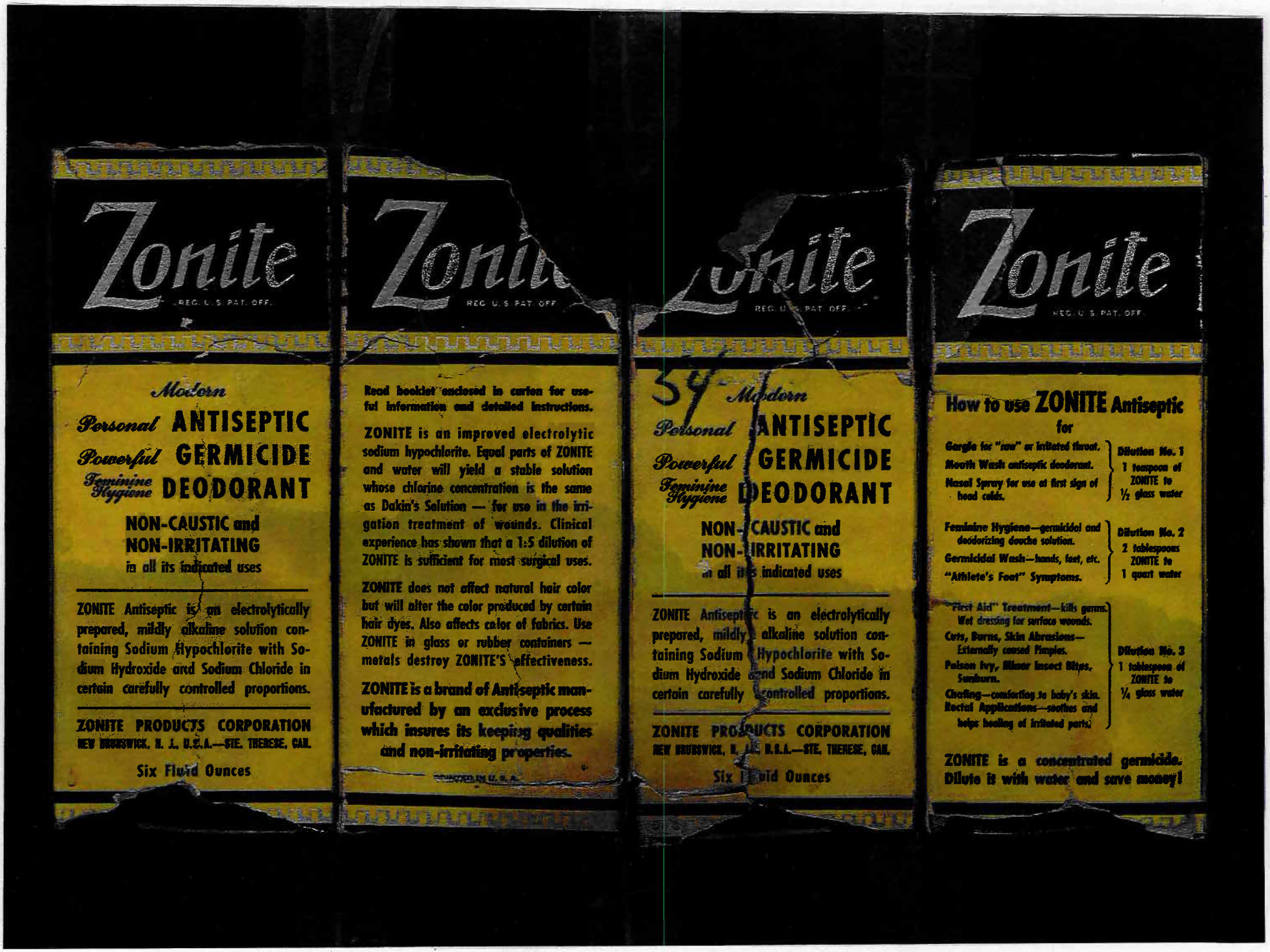
CP4, CP13, LET 41	22. Keen, W. W.	Description of the use of and preparation of Dakin's solution for wound irrigation. No information relevant to the marketing conditions of a specific NaOCl product. Concentration of NaOCl cited: 0.50%
CP4, CP13, LET41	23. Mc Donnell, K. J. and Sculco, T. P.	Review article of the historical use of Dakin's solution. No information relevant to the marketing conditions of a specific NaOCl product. Concentration of NaOCl cited: 0.50%
CP4, CP13	26. Thomas. S.	Description of the use of Milton's solution to hydrolyze and dissolve necrotic tissue. No information relevant to the marketing conditions of a specific NaOCl product. No concentration of NaOCl provided.
CP4, CP13	27. Bloomfield, S. F. and Sizer, T.J.	Investigation of the use of Eusol formulations. No concentration of NaOCl provided.
CP4, CP13, LET 41	29. Raffensperger, J. G.	Letter to the editor regarding the use of NaOCl solutions for wound debridement. No information relevant to the marketing conditions of a specific NaOCl product. No concentration of NaOCl provided.
CP4, CP13, Let 41	30. Barese, S.	Letter to the editor regarding the use of NaOCl solutions for wound debridement. No information relevant to the marketing conditions of a specific NaOCl product. No concentration of NaOCl provided.
CP4, CP13, LET42, SUP9	31. The Merck Index, 7th ed., 1960	Description of the preparation and identity of NaOCl dilute solution. No information relevant to the marketing conditions of a specific NaOCl product. Concentration of NaOCl cited: 0.45 to 0.50%
CP4, CP13, C92/C22	32. The Merck Index, 7th ed., 1989 Exhibit 8 (C92 and C22)	Description of the preparation and identity of NaOCl dilute solution. No information relevant to the marketing conditions of a specific NaOCl product. Concentration of NaOCl cited: 0.45 to 0.50%
CP4, CP13, LET42	33. Handbook of Nonprescription Drugs, 5th ed. 1977	Listing for concentrated (5.0%) and diluted (0.5%) NaOCl solutions. No information relevant to the marketing conditions of a specific NaOCl product. Date of reference after 1975.
CP4, CP13	34. Handbook of Nonprescription Drugs, 6th ed. 1979	Listing for concentrated (5.0%) and diluted (0.5%) NaOCl solutions. No information relevant to the marketing conditions of a specific NaOCl product. Date of reference after 1975.
CP4, CP13, LET 42, SUP9	35. Handbook of Nonprescription Drugs, 7th ed. 1979	Listing for concentrated (5.0%) and diluted (0.5%) NaOCl solutions. No information relevant to the marketing conditions of a specific NaOCl product. Date of reference after 1975.

CP4, CP13, LET42, SUP9	36. Remington's Practice of Pharmacy, 7th ed., 1936	Description of the preparation and identity of NaOCl dilute solution. No information relevant to the marketing conditions of a specific NaOCl product. Concentration of NaOCl cited: 0.45 to 0.50%. Use as a germicide for the treatment of wounds cited.
CP4, CP13, LET42, SUP9, MM7/MM1, C92/C22	37. Remington's Practice of Pharmacy, 9th ed., 1948	Description of the preparation and identity of NaOCl dilute solution. No information relevant to the marketing conditions of a specific NaOCl product. Concentration of NaOCl cited: 0.45 to 0.50%. Use as a germicide for the treatment of wounds.
CP4, CP13	38. The Pharmacopoeia of the United States, 10th ed., 1926	Description of the preparation and identity of Surgical Solution of Chlorinated Soda (Modified Dakin's Solution). No information relevant to the marketing conditions of a specific NaOCl product. Concentration of NaOCl cited: 0.45 to 0.50%.
CP4, CP13	39. The Pharmacopoeia of the United States, 11th ed., 1936	Description of the preparation and identity of Diluted Solution of Sodium Hypochlorite (Modified Dakins Solution). No information relevant to the marketing conditions of a specific NaOCl product. Concentration of NaOCl cited: 0.45 to 0.50%.
CP4, CP13, LET42, SUP9, C92/C22	40. Modern Drug Encyclopedia and Therapeutic Guide, 1934.	Description of Hychlorite. Provides information on the NaOCL concentration (4.05%) and uses of the product. The uses listed involve treatment of wounds and serious infections. The statement "for topical use and swabs -half or full strength," which appears in this reference, does not establish that this product was intended for patient preoperative use. Further, this product at one-half and full-strength would equal a 2.025 and a 4.05% use concentration, respectively.
CP4, CP13, LET42	41. Modern Drug Encyclopedia and Therapeutic Guide, 1941.	Description of Hychlorite. Provides information on the NaOCL concentration (4.05%) and uses of the product. The uses listed involve treatment of wounds and serious infections. The statement "for topical use and swabs -half or full strength," which appears in this reference, does not establish that this product was intended for patient preoperative use. Further, this product at one-half and full-strength would equal a 2.025 and a 4.05%use concentration, respectively.
CP4, CP13, LET42, MM7/MM1, C92/C22	42. Blue Book, 1946 Exhibit 39 (C92)	Listing for Hychlorite that describes the product as an antiseptic, deodorant, and germicide. Provides no other relevant information on the marketing conditions of the product.

CP4, CP13, LET42, MM7/MM1	43. Red Book, 1945 to 1946	Listing for Hychlorite. Provides no other relevant information on the marketing conditions of the product. No concentration of NaOCl provided.
CP4, CP13, LET42	44. Physician's Desk Reference, 1947	Listing for Hychlorite. Provides no other relevant information on the marketing conditions of the product. No concentration of NaOCl provided.
CP4, CP13	45. Red Book, 1992.	Listing for Dakin's Solution. Provides no other relevant information on the marketing conditions of the product. Reference date after 1975. No concentration of NaOCl provided.
CP4, CP13	46. Handbook of Nonprescription Drugs, 10th ed., 1993.	Listing for full (0.5%) and half (0.25%) strength Dakin's solution. Reference date after 1975.
CP4, CP13	47. Nonprescription Products: Formulations and Features, 1997	Listing for full (0.5%) and half (0.25%) strength Dakin's solution. Reference date after 1975.
MM7/MM1	Attachment 3. Red Book, 1946 to 1946	Listing for NaOCl solution. Provides no other relevant information on the marketing conditions of the product. No concentration of NaOCl provided.
MM7/MM1	Attachment 4, Red Book, 1945 to 1946	Listing for Zonite. Describes Zonite as a stable, concentrated, electrolytic sodium hypochlorite solution, an improvement on the famous Carrel-Dakin Solution discovered during World War I. It lists the product's properties as an "antiseptic, germicide, fungicide, deodorant, cleansing, and promotes healing," and states that the product is used for cuts, burns, bruises, poison ivy, minor insect bites, and wet dressing for wounds. These statements do not represent that the product was useful as a patient preoperative skin preparation, but could be considered representations for OTC first aid antiseptic use. However, these citations do not provide information on the formulation (e.g. explanation of the terms "stable" and "electrolytic") or the concentration of the active ingredient.
MM7/MM1, C92/C22	Attachment 6 (MM7), Exhibit 7 (C92) Survey of State Pharmacy Laws, 1958	A review of Minnesota State Board of Regulations. Lists antiseptics containing NaOCl as products that can only be a dealer licensed under the authority of Minnesota Statutes 1949. The reference provides no information on a specific NaOCl product. No concentration of NaOCl provided.

MM7/MM1, C92/C22	Attachment 7 (MM7/MM1), Exhibit 1(C92/C22) Article on top advertisers.	Lists expenditures of leading national advertisers. This reference simply identifies the Zonite Products Company as number 99 on a list of company expenditures for advertising in newspapers. This listing does not state what product(s) were being advertised for nor does it not provide adequate information relevant to the formulation, labeling, and commercial OTC marketing of Zonite prior to December 4, 1975. No concentration of NaOCl provided.
C92/C22	Exhibit 4 Red Book, 1945 to 1946	Listings for Dakin's Solution, NaOCL solution, and Zonite. See comments on Attachment 4 of MM7/MM1 for Zonite. Provides no other relevant information on the marketing conditions of the other products. No concentration of NaOCl provided.
C92/C22	Exhibit 9 American Drug Index, 1968	Listing for Dakin's solution. Provides no other relevant information on the marketing conditions of the other products. No concentration of NaOCl provided.

cc: (Docket No. 1975N-183H/CP13 and 1975N-183F/CP4)
HFC-1
HFC-230: DCP File Room
HFC-230: L Pallas
HFA-305: Division of Dockets Management
HFD-1: Director, CDER
HFD-020: Director, OND
HFD-006: Barbara Palm
Office of Chief Counsel
Office of Regulatory Affairs
Office of Nonprescription Drugs
Division of Nonprescription Regulation Development



Zonite
REG. U. S. PAT. OFF.

Modern
Personal **ANTISEPTIC**
Powerful **GERMICIDE**
Feminine Hygiene **DEODORANT**

NON-CAUSTIC and NON-IRRITATING
in all its indicated uses

ZONITE Antiseptic is an electrolytically prepared, mildly alkaline solution containing Sodium Hypochlorite with Sodium Hydroxide and Sodium Chloride in certain carefully controlled proportions.

ZONITE PRODUCTS CORPORATION
NEW BRUNSWICK, N. J., U.S.A.—STE. THERESE, CAN.

Six Fluid Ounces

Zonite
REG. U. S. PAT. OFF.

Read booklet enclosed in carton for useful information and detailed instructions.

ZONITE is an improved electrolytic sodium hypochlorite. Equal parts of ZONITE and water will yield a stable solution whose chlorine concentration is the same as Dakin's Solution — for use in the irrigation treatment of wounds. Clinical experience has shown that a 1:5 dilution of ZONITE is sufficient for most surgical uses.

ZONITE does not affect natural hair color but will alter the color produced by certain hair dyes. Also affects color of fabrics. Use ZONITE in glass or rubber containers — metals destroy ZONITE'S effectiveness.

ZONITE is a brand of Antiseptic manufactured by an exclusive process which insures its keeping qualities and non-irritating properties.

PRINTED IN U. S. A.

Zonite
REG. U. S. PAT. OFF.

59¢

Modern
Personal **ANTISEPTIC**
Powerful **GERMICIDE**
Feminine Hygiene **DEODORANT**

NON-CAUSTIC and NON-IRRITATING
in all its indicated uses

ZONITE Antiseptic is an electrolytically prepared, mildly alkaline solution containing Sodium Hypochlorite with Sodium Hydroxide and Sodium Chloride in certain carefully controlled proportions.

ZONITE PRODUCTS CORPORATION
NEW BRUNSWICK, N. J., U.S.A.—STE. THERESE, CAN.

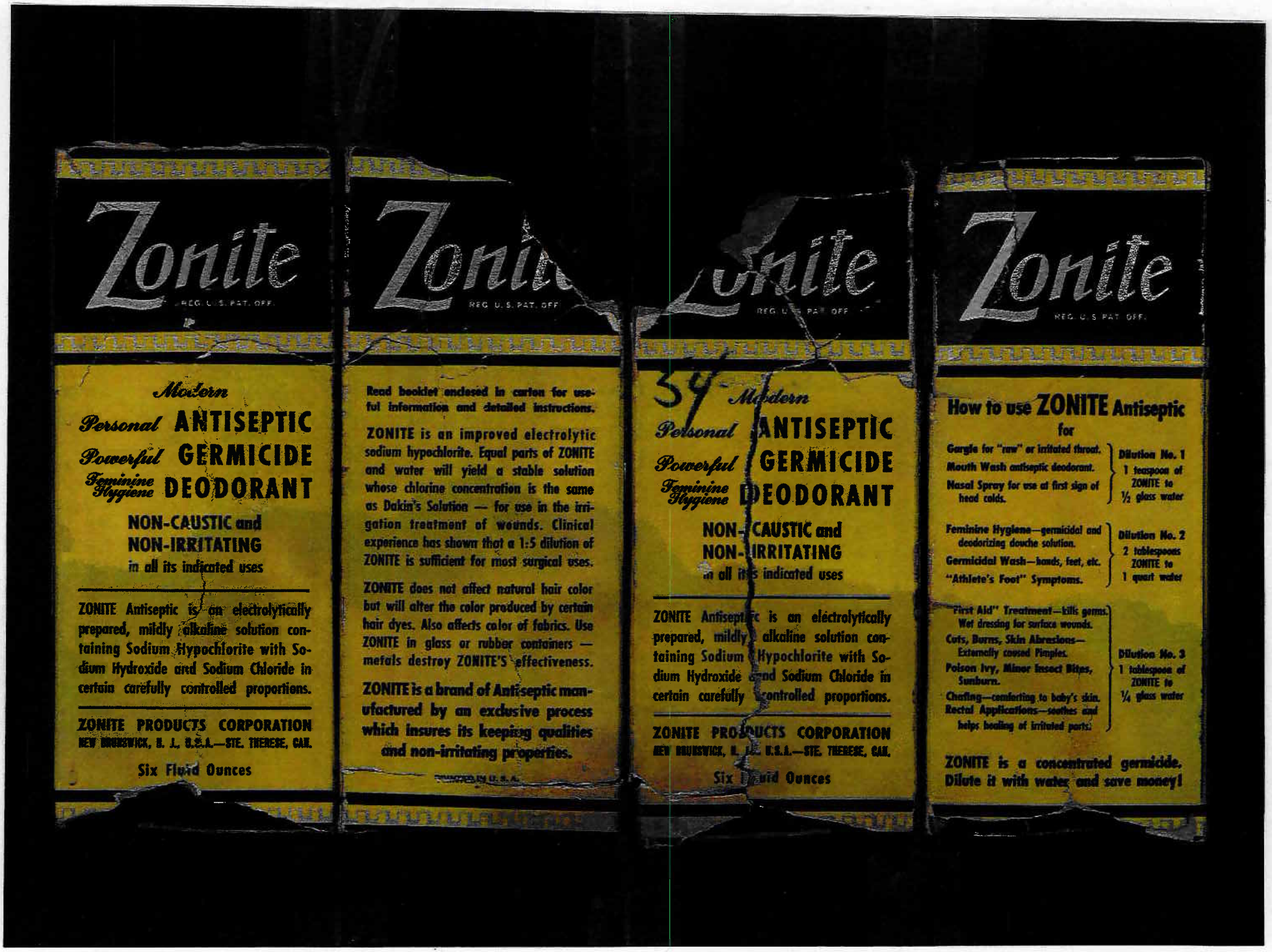
Six Fluid Ounces

Zonite
REG. U. S. PAT. OFF.

How to use ZONITE Antiseptic for

Gargle for "raw" or irritated throat. Mouth Wash antiseptic deodorant. Nasal Spray for use at first sign of head colds.	Dilution No. 1 1 teaspoon of ZONITE to ½ glass water
Feminine Hygiene—germicidal and deodorizing douche solution. Germicidal Wash—hands, feet, etc. "Athlete's Foot" Symptoms.	Dilution No. 2 2 tablespoons ZONITE to 1 quart water
"First Aid" Treatment—kills germs. Wet dressing for surface wounds. Cuts, Burns, Skin Abrasions—Externally caused Pimples. Poison Ivy, Minor Insect Bites, Sunburn. Chafing—comforting to baby's skin. Rectal Applications—soothes and helps healing of irritated parts.	Dilution No. 3 1 tablespoon of ZONITE to ¼ glass water

ZONITE is a concentrated germicide. Dilute it with water and save money!



Zonite

REG. U.S. PAT. OFF.

Modern
Personal **ANTISEPTIC**
Powerful **GERMICIDE**
Feminine Hygiene **DEODORANT**

NON-CAUSTIC and NON-IRRITATING
in all its indicated uses

ZONITE Antiseptic is an electrolytically prepared, mildly alkaline solution containing Sodium Hypochlorite with Sodium Hydroxide and Sodium Chloride in certain carefully controlled proportions.

ZONITE PRODUCTS CORPORATION
NEW BRUNSWICK, N. J., U.S.A.—STE. THERESE, CAN.

Six Fluid Ounces

Zonite

REG. U.S. PAT. OFF.

Read booklet enclosed in carton for useful information and detailed instructions.

ZONITE is an improved electrolytic sodium hypochlorite. Equal parts of ZONITE and water will yield a stable solution whose chlorine concentration is the same as Dakin's Solution — for use in the irrigation treatment of wounds. Clinical experience has shown that a 1:5 dilution of ZONITE is sufficient for most surgical uses.

ZONITE does not affect natural hair color but will alter the color produced by certain hair dyes. Also affects color of fabrics. Use ZONITE in glass or rubber containers — metals destroy ZONITE'S effectiveness.

ZONITE is a brand of Antiseptic manufactured by an exclusive process which insures its keeping qualities and non-irritating properties.

PRINTED IN U.S.A.

Zonite

REG. U.S. PAT. OFF.

Modern
Personal **ANTISEPTIC**
Powerful **GERMICIDE**
Feminine Hygiene **DEODORANT**

NON-CAUSTIC and NON-IRRITATING
in all its indicated uses

ZONITE Antiseptic is an electrolytically prepared, mildly alkaline solution containing Sodium Hypochlorite with Sodium Hydroxide and Sodium Chloride in certain carefully controlled proportions.

ZONITE PRODUCTS CORPORATION
NEW BRUNSWICK, N. J., U.S.A.—STE. THERESE, CAN.

Six Fluid Ounces

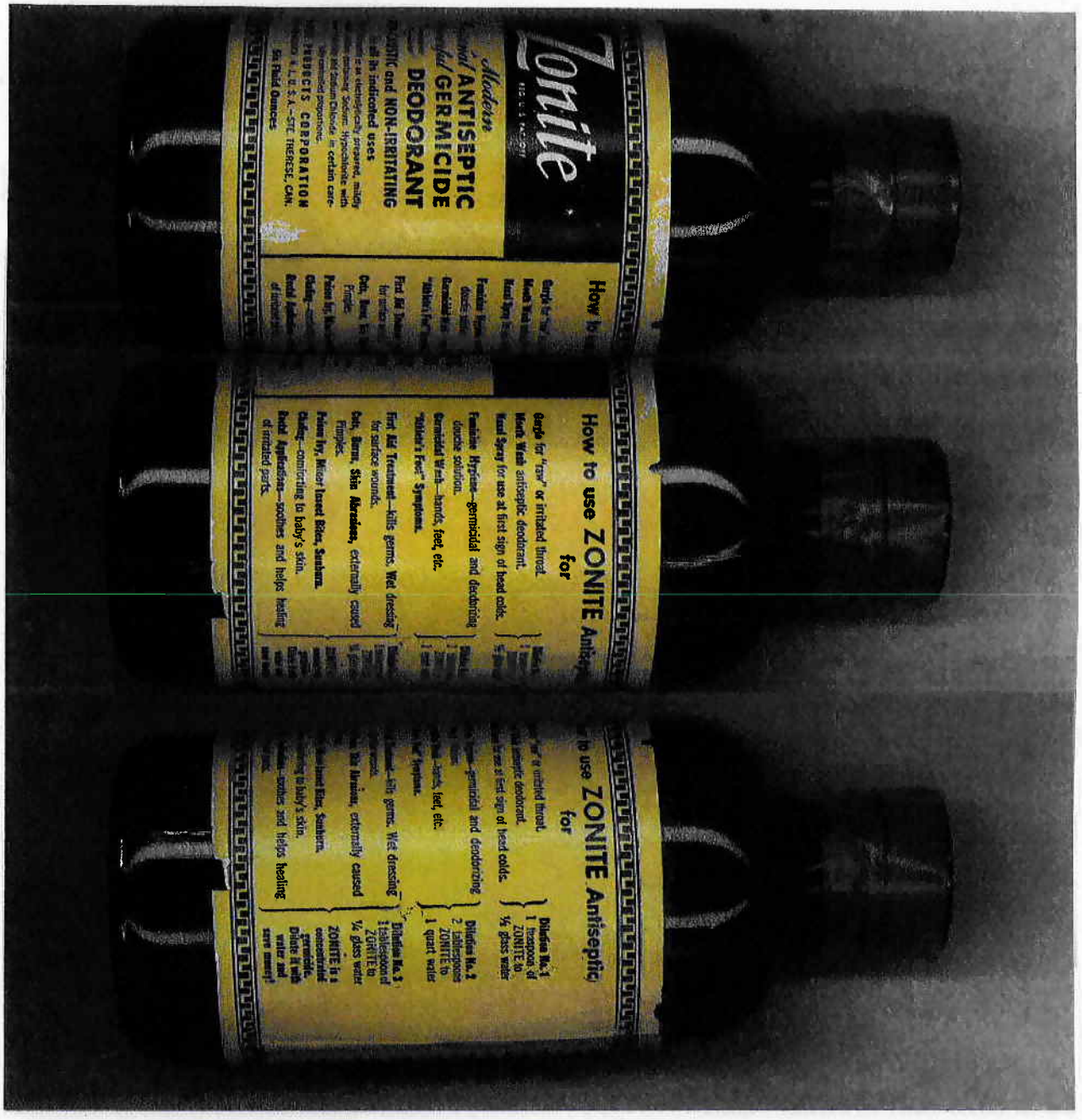
Zonite

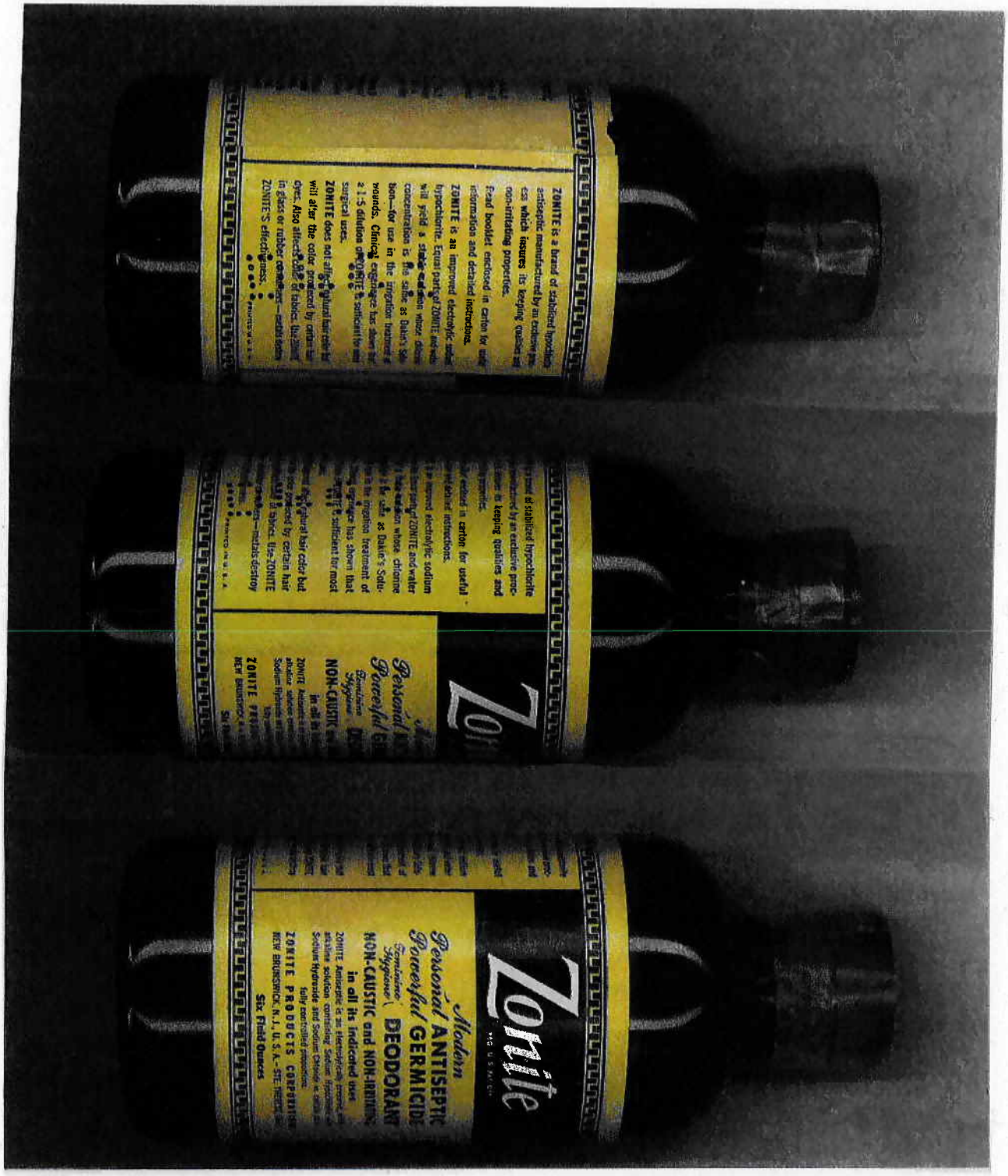
REG. U.S. PAT. OFF.

How to use ZONITE Antiseptic for

Gargle for "raw" or irritated throat. Mouth Wash antiseptic deodorant. Nasal Spray for use at first sign of head colds.	Dilution No. 1 1 teaspoon of ZONITE to ½ glass water
Feminine Hygiene—germicidal and deodorizing douche solution. Germicidal Wash—hands, feet, etc. "Athlete's Foot" Symptoms.	Dilution No. 2 2 tablespoons ZONITE to 1 quart water
"First Aid" Treatment—kills germs. Wet dressing for surface wounds. Cuts, Burns, Skin Abrasions—Externally caused Pimples. Poison Ivy, Minor Insect Bites, Sunburn. Chafing—comforting to baby's skin. Rectal Applications—soothes and helps healing of irritated parts.	Dilution No. 3 1 tablespoon of ZONITE to ¼ glass water

ZONITE is a concentrated germicide. Dilute it with water and save money!


Zonite
Modern ANTISEPTIC and GERMICIDE DEODORANT
ANTISEPTIC and NON-IRRITATING
How to use ZONITE Antiseptic for
Gargle for "raw" or irritated throat.
Mouth Wash antiseptic deodorant.
Nasal Spray for use at first sign of head colds.
Douche Solution—germicidal and deodorizing
Douche solution.
Diluted Wash—hands, feet, etc.
"Athlete's Foot" Symptoms.
First Aid Treatment—kills germs. Wet dressing
for surface wounds.
Cuts, Burns, Skin Abrasions, externally caused
Pimples.
Poison Ivy, Minor Insect Bites, Sunburn.
Chafing—convincing to baby's skin.
Rectal Application—soothes and helps healing
of irritated parts.
PRODUCTS CORPORATION
Six Fluid Ounces


ZONITE is a brand of stabilized hypochlorite
antiseptic manufactured by an exclusive pro-
cess which insures its keeping qualities as
non-irritating properties.
Read booklet enclosed in carton for useful
information and detailed instructions.
ZONITE is an improved electrolytic solu-
hypochlorite. Equal parts of ZONITE and wa
will yield a stable solution whose chlorine
concentration is the same as Dakin's solu-
tion—for use in the irrigation treatment o
wounds. Clinical experience has shown tha
2 1-5 dilution of ZONITE is sufficient for mo
surgical uses.
ZONITE does not affect natural hair color bu
will alter the color produced by certain hair
dyes. Also affects some fabrics. Use ZONITE
in glass or rubber containers—metals destroy
ZONITE'S effectiveness.
Zonite
Personal ANTISEPTIC
Powerful GERMICIDE
Feminine Hygiene DEODORANT
NON-CAUSTIC and NON-IRRITATING
in all its indicated uses
ZONITE Antiseptic is an electrolytically created
alkaline solution containing Sodium Hypochlorite
Sodium Hydroxide and Sodium Chloride in carefully
fully controlled proportions
ZONITE PRODUCTS CORPORATION
NEW BRUNSWICK, N. J., U. S. A.—SEE INSIDE
Six Fluid Ounces