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March 15, 2004

VIA HAND DELIVERY

Daniel E. Troy, Esquire
Chief Counsel
U.S. Food and Drug Administration
Parklawn Building, Room 605 (GCF-1)
5600 Fishers Lane
Rockville, Maryland 20857

Re: Meeting with Alcavis International, Inc regarding Citizen Petitions – Docket No. 75N-183H Comment No. CP13 and Docket No. 75N-183F Comment No. CP4

Dear Mr. Troy:

This letter on behalf of Alcavis International, Inc. provides a follow-up to our February 12, 2004 meeting. The meeting provided an opportunity for Alcavis to discuss the lack of action by the Division of OTC Drug Products on two Alcavis citizen petitions regarding OTC review of sodium hypochlorite as a topical antiseptic ingredient. During that meeting you raised a few questions regarding the scope of the OTC monographs, and the historical use of sodium hypochlorite. This letter addresses those questions.

As you know, Alcavis has submitted two citizen petitions for review of the active ingredient sodium hypochlorite. One petition is for review of the ingredient under the monograph for OTC first aid antiseptics, and the second is for review of the ingredient under the OTC healthcare antiseptic monograph. The information in this letter applies broadly to both monographs, though with a focus on the healthcare antiseptic monograph.

One question raised during the meeting was whether sodium hypochlorite was used prior to 1972 in a manner consistent with the indications the OTC healthcare antiseptic monograph. You also asked whether use as a hospital product for administration by healthcare workers constitutes OTC use, and whether the historic use supports inclusion in the healthcare antiseptic monograph as a preoperative skin preparation antiseptic. You also requested that Alcavis provide additional historical evidence of commercial marketing of sodium hypochlorite based antiseptics. We will address this additional historical evidence first.

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Commercial Marketing of Sodium Hypochlorite as an OTC Antiseptic Ingredient

As discussed at the meeting, and in our February 2, 2004 letter, sodium hypochlorite has been widely used as a general antiseptic and disinfectant. Due to sodium hypochlorite's relatively easy preparation, and the short shelf-life of some hypochlorite formulations, pharmacies commonly compounded the solution prior to use rather than purchase pre-made solutions of the drug. Nevertheless, there were several commercial solutions available. In the petitions and the various letters to FDA, Alcavis has provided evidence of historic use, including marketing of "Hyclorite," a sodium hypochlorite concentrate manufactured by Bethlehem Laboratories (attachment 1). As reflected in those materials, Hyclorite was used for a variety of antiseptic and disinfectant uses, including indications appropriate to both the healthcare and first aid antiseptic monographs (discussed later in this letter). Alcavis also provided references to various pharmacy texts that discuss sodium hypochlorite's preparation, antimicrobial effect, and its use as a topical antiseptic.

This evidence alone is legally sufficient to support inclusion of sodium hypochlorite in the OTC topical antiseptic monographs. However, at your request, we are providing additional historical evidence of commercial use. Despite the difficulty in finding materials from over one half century ago, there is still significant evidence of the professional and commercial use of sodium hypochlorite as an antiseptic.

1945-1946 Red Book

The 1945-1946 Red Book has at least three separate references for commercially available sodium hypochlorite products. This book provides pharmacy product information including manufacturer's products and prices.

Attachment 2 is page 128 from the 1945-1946 Red Book. On this page there is a listing for 3 ounce "Dakin's Solution." Dakin's solution the sodium hypochlorite solution first used as a wound antiseptic in World War I, and subsequently used for a variety of medical antiseptic and disinfectant indications. Alcavis' citizen petitions provide details on Dakin's solution and its uses.

Attachment 3 is page 315 from the same 1945-1946 Red Book. This page has a listing for "Sodium Hypochlorite Solution USP" from Merck. Historic USP references for sodium hypochlorite were also provided in Alcavis' citizen petitions.

Attachment 4 is page 384 of the same 1945-1946 Red Book. this page has a listing for "Zonite." The listing states that "Zonite is a stable, concentrated, electrolytic sodium hypochlorite solution, an improvement on the famous Carrel-Dakin Solution discovered during World War I." It is listed as "antiseptic, germicide, fungicide, deodorant, cleansing, promotes healing," and is "used for ... cuts, burns or bruises; poison ivy; minor insect bites; ... wet dressing for wounds."

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1948 Edition of Remington's Practice of Pharmacy

Page 333 (attachment 5) has a listing for "Diluted Sodium Hypochlorite Solutions," and lists among the uses, treatment of wounds. Both Hychlorite and Zonite are listed as commercial sodium hypochlorite preparations.

A Survey of State Pharmacy Laws (1958 Edition)

Page 74 of this state-by-state survey of nonprescription drug pharmacy laws (attachment 6) provides a list of drug ingredients by therapeutic category. The listing for antiseptics includes both "Sodium Hypochlorite" and "Zonite." Entries for other states do not provide drug ingredients listed by therapeutic categories.

Article on top advertisers in 1924

Attachment 7 is an article that contains information provided by Crowell Publishing Company, listing the expenditures of leading national advertisers in thirty magazines. Number 99 on the list is Zonite Products Co. This listing provides solid evidence of significant marketing and commercial distribution of Zonite, a sodium hypochlorite antiseptic.

Hospital Use of Sodium Hypochlorite

During our meeting, you questioned whether a drug, such as sodium hypochlorite, that was historically used by healthcare professionals rather than directly by consumers, may appropriately be reviewed under an OTC monograph. As discussed above, while sodium hypochlorite was widely used by healthcare professionals in clinical settings, it was also used by and sold to the general public. However, even if it had only been readily available to healthcare professionals, it still would properly be considered an OTC antiseptic. FDA directly addressed this issue in the January 6, 1978 tentative final monograph for OTC topical antimicrobial products (43 Fed. Reg. 1210). On page 1215, FDA responded to a comment objecting to classification of a patient preoperative skin preparation as an OTC product. The objection was that "the surgeon usually 'prescribes' for his patient the types of antimicrobial to be employed in preparing the site of incision." FDA responded:

"Prescribe" can mean to specify use of a drug legally restricted to dispensation, or simply to specify with authority. It is common for physicians, on the basis of their professional knowledge, to direct the use of various products, such as OTC drugs and certain foods, that are not limited to prescription sale. The OTC or prescription status of patient preoperative skin preparations or surgical hand scrubs, therefore, does not affect the surgeon's ability to control what products will be used to prepare his patient for surgery or by those participating in the procedure. Nor does it relate to the effectiveness of the products. The difference between an OTC or prescription product

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does not lie in effectiveness, but in whether or not it can be labeled for safe and effective use by the lay person. Since patient preoperative skin preparations and surgical hand scrubs can be so labeled for use by health care personnel, there is no reason to reclassify them as prescription drugs.

As a result, the dispensation of sodium hypochlorite by hospital pharmacies, and the use by healthcare professionals does not change the status of the drug from OTC to prescription. Simply put, if a drug is not restricted to dispensing by or on the order of a physician, it is an OTC drug.

Additional support for OTC status for products used by healthcare personnel is provided by the proposed 21 CFR § 333.99 for professional labeling of OTC antiseptic ingredients (43 Fed Reg. at 1248). OTC drugs labeled in accordance with this section would be for use by health professionals, primarily in healthcare facilities.

OTC Healthcare Antiseptic Indications

Another question that has been raised by FDA is whether the historic use of sodium hypochlorite is compatible with the indications being reviewed under the OTC healthcare antiseptic monograph. As was stated in the February 2, 2004 letter, specific indications under the healthcare antiseptics monograph were somewhat arbitrary. Prior to the initiation of the OTC review, it was not uncommon for antiseptics (such as sodium hypochlorite) to be indicated generally for antiseptic, disinfectant and germicidal use. Such indications would have been understood to include the specific indications listed in the current monograph. The definition of product categories, as used in the monographs, were developed by the OTC review panel in recognition that not all uses of topical antiseptics need meet the same effectiveness criteria (39 Fed Reg. 33103 at 33114, September 13, 1974). The discrete categories facilitated the development of appropriate effectiveness testing for each type of antiseptic. The categories were not intended to exclude a product on the grounds that its general antiseptic labeling did not specifically describe a particular antiseptic use.

The term "preoperative skin preparation" does not adequately describe the various antiseptic uses that are meant to be included within the definition. For example, the preamble to the tentative final monograph expressly provides that preoperative skin preparation includes antisepsis of the skin prior to the insertion of catheters, as well as disinfection of the part of the device that contacts the skin (43 Fed. Reg. at 1225). Therefore, it is clear that the definition of preoperative skin preparation must be read broadly.

Sodium hypochlorite, while not specifically labeled for "preoperative skin preparation," was labeled generally for use on wounds, and more specifically, Hychlorite was indicated for (among other things) "surgery." From historical documents (such as those included in the petitions) it is clear that use for surgery entails cleansing of both wounds and skin. This use falls clearly within the intended scope of the preoperative skin preparation indication.

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Reopening of the Administrative Record

Alcavis' petitions request that FDA reopen the administrative record of the First Aid and Healthcare Antiseptic Monographs to permit consideration of sodium hypochlorite. Alcavis believes that failure to accept its petitions for review would constitute an arbitrary and capricious abuse of discretion on the part of FDA. The OTC monograph system was designed as a fair and equitable alternative to individual review of the vast number of OTC products that were on the market at the time the review was initiated. The glacial pace of FDA's review of these monographs has led to several instances where fairness and public interest have caused FDA to reopen the monographs to allow consideration of new comments and information. Therefore, FDA has set the precedent that it accept additional information into the monographs. Most applicable to the issues in this letter, in 2003, FDA opened the record to consider a petition from the Soap and Detergent Association (SDA) and The Cosmetic, Toiletry, and Fragrance Association (CTFA) to amend the healthcare antiseptics monograph (68 Fed. Reg. 32003, May 29, 2003). Meanwhile, Alcavis' petitions to reopen the record have been either rejected without significant review or ignored. This disparity in treatment is an arbitrary and capricious abuse of the Agency's discretion. The OTC monograph system does not exist solely for the benefit of large trade associations.

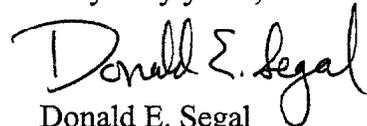
Actions Requested

Alcavis believes that its petitions provide more than enough legal, regulatory, historic and scientific support for their acceptance for review as part of the monograph processes. The information provided in recent correspondence with the agency provides additional support for their acceptance. FDA should expeditiously accept the petitions and thereafter conduct a thorough review of the issues therein, and provide a response that addresses the actual contents of the petitions. Alcavis believes that such acceptance and review will support conclusions that sodium hypochlorite is generally recognized as safe and effective for use under both the OTC First Aid Antiseptic and OTC Healthcare Antiseptic Monographs. Positive action on these petitions, and the continued availability of this safe and effective antiseptic agent, is of the highest importance to Alcavis and its healthcare customers.

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If you have any questions, or wish to discuss the matter further, please contact me at 202-452-7959. We look forward to your favorable response.

Very truly yours,

A handwritten signature in black ink that reads "Donald E. Segal". The signature is written in a cursive style with a large, prominent "D" and "S".

Donald E. Segal
Robert G. Pinco
Theodore M. Sullivan

Enclosures

cc: First Aid Antiseptic Monograph, Docket No. 75N-183F
Healthcare Antiseptic Monograph, Docket No. 75N-183H