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June 5, 2003

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VIA FACSIMILE AND CERTIFIED MAIL

Ms. Michelle M. Jackson
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Alcavis International Inc. Citizen Petition – Docket No. 75N-183H Comment No. CP13

Dear Ms. Jackson:

As we discussed last week, I have enclosed the two letters submitted by Alcavis International on December 20, 2002 and March 18, 2003 responding to Mr. Taylor's earlier letter of November 14, 2002. Copies of both letters were sent to Docket No. 75N-183H. From our discussion, however, it appears that one or both letters may not have been placed in the docket or reviewed by your office.

Without restating Alcavis' position in detail, the Petition and enclosed correspondence provide ample evidence that sodium hypochlorite is appropriate for review under the Healthcare Antiseptic monograph and that the filing of a Time and Extent of the Application would be both unnecessary and inappropriate. As further explained, sodium hypochlorite has been used since as early as World War I and has been utilized in marketed products since the 1940s. See letter of March 18, 2003 and Citizen's Petition of February 20, 2002, especially Exhibit Nos. 31-44. I am providing a copy of the Petition by separate mailing.

Alcavis has expended significant resources and energy in preparing its Petition and responding to Mr. Taylor's correspondence. It does not appear that the Petition and subsequent correspondence have been reviewed to any meaningful degree. The action requested in the Petition is of great importance to the company and merits full and fair consideration by the agency. Alcavis requests an acknowledgement that action requested in its Citizen Petition will be reconsidered. Of course we are available to discuss further, answer any questions or meet with appropriate officials.

Very truly yours,

Donald E. Segal

Donald E. Segal

Enclosures

cc: Docket No. 75N-183H
Mr. John M. Taylor
Mr. Tom Chin

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March 18, 2003

John M. Taylor, III
Associate Commissioner for Regulatory Affairs
Food and Drug Administration
Parklawn BLdg., rm. 1490 (HFC-1)
Rockville, MD 20857

Re: Alcavis International, Inc. Citizen Petition –Docket No. 75N-183H
Comment No. CP13

Dear Mr. Taylor:

This letter is in response to your letter dated November 14, 2002 and following an interim response dated December 20, 2002 notifying you that we would be forwarding a more complete response regarding the use of Alcavis' product as a patient preoperative skin preparation. The information presented in this letter provides a general outline of the information included in the Citizen Petition filed with the Agency on February 20, 2002, which requested that the active ingredient, sodium hypochlorite 0.1% to 0.5%, be included as a patient preoperative skin preparation in the Over – the – Counter ("OTC") monograph for the Healthcare Antiseptic Drug Products.[1]

As you know, a Tentative Final Monograph ("TFM") for Healthcare Antiseptic Drug Products was published on June 17, 1994.[2] In the TFM, healthcare antiseptic is defined as "an antiseptic containing drug product applied

[1] See, Federal Register of June 17, 1994, vol. 59, p. 31402. (52 FR 31402).
[2] Id.

topically to skin to help prevent cross contamination."[3] The monograph provides three specific uses for healthcare antiseptic: (1) patient preoperative skin preparation; (2) antiseptic handwash or healthcare personnel handwash; and (3) surgical hand scrub.

There has been a dramatic increase in the prevalence of devices used that require routine site changes and care since the publication of this document. Alcavis has always been interested in site access and care which is briefly considered in the June 17, 1994 monograph describing preparation for injection and is subsumed under the patient pre-operative preparation.

As explained below, sodium hypochlorite is appropriate for the Agency to review under the Healthcare Antiseptic monograph. Furthermore, the facts associated with the use and U. S. marketing history of this ingredient do not comport with the requirements for filing a Time and Extent Application ("TEA") and, a request to file such an application is contrary to the regulations.

I. HISTORIC USE OF SODIUM HYPOCHLORITE

Sodium hypochlorite in various concentrations has had a long history of use. In fact, Dr. Alexis Carrel, a Nobel laureate and renowned chemist, Henry Dakin, formulated a solution that consisted of 0.45% to 0.5% sodium hypochlorite to combat the high mortality rate as a result of wound infection during the World War I. This solution became known as Dakin's solution.[4] The history of use of

[3] Id. at 31442.
[4] See, Citizen Petition pages 9-10 for references that provide descriptions of Dakin's Solution.

products like Dakin's prior to surgery or indeed, whenever the integrity of the skin is breeched, is important in understanding the development of categories for antimicrobial products developed by the OTC Antimicrobial Panel as well as the use of products marketed early in the history of skin antisepsis/disinfection with antimicrobial agents. The long historic use of Dakin's sodium hypochlorite solution provides extensive clinical use of it as a skin preparation prior to treatment and for access site as described in our Petition, references 6, 21, 22 and is referred to and discussed as a preoperative preparation in the Petition text, page 41 and following. In use, the Carrel/Dakin procedure required a series of tubes inserted into contaminated deep wounds and arranged so that new sodium hypochlorite solution from a reservoir could be percolated intermittently into the wound. The patient's skin and wound margins were cleansed and treated (prepped) with Dakin's prior to the insertion and arrangement of tubes for further treatment. This solution and its use are described in more detail through our Citizen Petition and is explained further in the references as cited.[5]

In the development of the TFM (June 17, 1994), the definition of Skin Antiseptic has changed from a topically applied antimicrobial that "prevents infection" to the current general definition of a skin antiseptic and the refined healthcare definitions. Prior to these OTC definitions of antiseptic products categories, many antimicrobials for skin use were marketed as a "general skin antiseptic" and used in many different ways, and often sold as a concentrate and diluted in use. As an example, with this "general" definition prior to the 1950s several products like alcohol, sodium hypochlorite, phenol products (PCMX) and

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[5] See, Citizen Petition pages 8-9, and 40-44, and references 6, 21-22.

[6] As seen with para-chloro-meta xylenol (PCMX), the use of an antiseptic product may evolve over time and as the needs of the healthcare industry shift. PCMX is another old ingredient with extensive use both as a disinfectant (on hard surfaces) and as an antiseptic on skin and mucous tissue. There are many similarities in use and evolution between PCMX and sodium hypochlorite.

tincture of green soap were used on skin prior to surgery and marketed and labeled for care of the skin prior to treatment and/or surgical procedures among numerous other topical uses and were often called a skin antiseptic[6]. The very specific definition of a product as a pre-operative preparation was made by the OTC Antimicrobial Panel in 1972. Prior to this, the widely used ingredients named above and newer (1950s) ones like iodophor and hexachlorophene were used to prepare skin for injection and surgery and for use prior to surgical procedures of all kinds including irrigation and pre-surgical bathing.

Prevention of post-surgical infection or treatment of them has always been the goal of use of pre-operative or treatment products but demonstration of this is rare. The Carrel/Dakin procedure was credited with saving may lives (Ref 5) and resulted in the lowest amputation rates for hospitals in France and Belgium in World War I. These results were the basis for the continued use of sodium hypochlorite in these procedures (Ref 3, 4, 7, 21, 22, 23) in the United States. This continued use in Europe, was discussed on page 8 of our Petition and was demonstrated in the United States in 1917 at the New Rockefeller Demonstration Hospital for War Training located on the grounds of Rockefeller Institute in New York. The method was well received in the United States and was used in civilian as well as military surgical practice. A clinical trial involving the incidence of post-operative infection as an outcome is essentially impossible to perform today because of multiple factors of antiseptic and sterile procedures and very low contamination and infection rates. Recent publication by Larson attempting to substantiate from the world literature prevention of post-surgical infection after use of presurgical antiseptic techniques with all types of preps failed for the reasons cited above. In contrast, the wounded soldiers from WWI trench warfare presented in the hospital with severe and heavily contaminated wounds and

relied on the use of physical debridement, Dakin's solution and the Dakin/Carrel procedure to preserve their life and limbs.

Geelhoed and Sharpe (1983, Petition Ref 107) have noted that, "skin preparation has not advanced much beyond those early milestones (Semmelweis, Lister and Halsted), with the ritual and rationale remaining essentially unchanged since the advent of asepsis." The OTC definitions may have been refined but the use and associated procedures have to be expanded to fit new uses as in the more generalized historical use.

The topical application of antimicrobials is preparation of the skin for whatever procedure or part or portion of patient is to be treated. Sodium hypochlorite has been used clinically as a skin antiseptic for pre-operative use and wound treatment since 1916 in World War I. There are both in vitro and laboratory clinical studies describing testing for pre-operative use and often tested and positively compared to iodophor formulations included in the Petition. Iodophors are the most commonly used pre-operative antiseptic in the U.S., if not worldwide. Sodium hypochlorite is equivalent to iodophors in these studies.

Another frequent use of Dakin's or similar hypochlorite formulations has been to prepare and treat skin ulcers (Petition ref. 7, 10, 23, 29, 30). These skin eruptions are cleaned and debrided with hypochlorite prior to surgical debridement and/or treatment with this or other antimicrobials/antibiotics. This use for skin preparation to reduce the microbial load on the skin prior to treatment to prevent further contamination and infection of the wound is certainly the definition of a pre-operative prep and a skin antiseptic.

Documentation that other sodium hypochlorite products began being marketed as early as the 1940s are listed and included in the petition:

1. HYCHLORITE in the mid 40s by Bethlehem Lab. Pittsburgh, PA.
2. Sodium Hypochlorite Solution Merck by Merck in the mid 40s, again.
3. Dakin's solution by Century Pharmaceuticals, Indianapolis, IN in the 90s.

Amuchina (now Alcavis) began marketing their own product in Italy in 1946. These products were very generally labeled for antiseptic use and were often diluted. Dakin's was a pharmacoepial item and was often prepared for use in the hospital by the pharmacist.

The initial applications of sodium hypochlorite as Dakin's solution in the irrigation procedure has led to the use of this ingredient as an antiseptic to disinfect connectors and treat the skin in peritoneal and hemodialysis as well as in preparation for surgery or injections.[6] These applications are preformed immediately before dialysis.[7] These developments require frequent and repeated treatments in their use.

II. PURPOSE OF TEA REGUALTIONS

As stated in the introduction to the regulations, the purpose of the TEA regulations is to provide "additional criteria and procedures by which OTC drugs initially marketed in the United States after the OTC drug review began in 1972

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[7] See attachment A for additional references or the use of sodium hypochlorite in dialysis.
[8] 21 C.F.R. 330.14

ALCAVIS INTERNATIONAL

and OTC drugs without any U.S. marketing experience can be considered in the OTC drug monograph system."[8] Therefore, it would be inappropriate to file a TEA for an active ingredient that can show U.S. marketing history for a specific OTC use prior to the OTC drug review.

Clearly, the use of sodium hypochlorite as described in the above sections demonstrates that the active ingredient was well in use prior to the OTC drug review. Indeed, based on the information provided, the use of sodium hypochlorite began in the early 1900s and continues today. Also, Alcavis International (formerly Amuchina) has been marketing a sodium hypochlorite product since 1945. For FDA to require that a TEA be filed for this ingredient would be contrary to the regulations.

For all of the foregoing reasons, the Agency's initial refusal to review the Citizen Petition is an error. The Agency's error can be easily remedied by reviewing the Alcavis Citizen Petition as it was submitted on February 20, 2002 and providing the appropriate provisions in the Healthcare Antiseptic Monograph.

In expectation that you will agree, we would appreciate a letter acknowledging that our Citizen Petition filed on February 20, 2002 has now been accepted for review. Alternatively, if there are any questions regarding the information contained in this letter or the Citizen Petition, we request a meeting to facilitate the Agency's understandings of these issues.

Sincerely,

Ludovico Giavotto

cc: Dockets Management Branch
(Docket N. 75N-183H)

ALCAVIS INTERNATIONAL

Mr. John M. Taylor
March 18, 2003
ADDENDUM A, Page 1

A list of published articles describing the use and effectiveness of sodium hypochlorite products in dialysis is listed below:

1) Buoncristiani and others. An ideal disinfectant for peritoneal dialysis (highly efficient, easy to handle and innocuous) NUA Vol. 1, Apr 1980: 45-48 *Comment: Buoncristiani is introducing the concept of preventing peritonitis in PD using a new kind of catheter combined with a disinfectant (Amuchina).*

2) Bianchi P., Buoncristiani U. Comparative in vitro study of three disinfectants (sodium hypochlorite, iodine, chlorhexidine). Their possible use in the treatment of peritonitis. NUA Proceedings of the 1st Italian Congress on CAPD, March 1981 *Comment: Buoncristiani background studies to propose the use of sodium hypochlorite in the Y sets.*

3) Maiorca R., Cantaluppi A. and others. Prospective controlled trial of a Y-connector and disinfectant to prevent peritonitis in Continuous Ambulatory Peritoneal Dialysis. Lancet 1983 Sept. 17; 2 (8351): 642-644 *Comment: prevention of the peritonitis in PD using a Y shaped catheter and Amuchina*

4) C. Cruz and others. Preoperative disinfection of the skin: Iodinated vs. chlorine compounds. Acta Toxicologica et Therapeutica XIV, 1: 1993; 1-8. *Comment: Antibacterial and degerming of the skin, microbiological test.*

5) Churchill D.N. Peritonitis in CAPD: a multicenter randomized clinical trial comparing the Y connector system to standard system. Peritoneal Dialysis International 9, 159-163, 1989. *Comment: prevention of the peritonitis in PD using a Y shaped Catheter and Amuchina.*

6) Dasgupta M.K. – Y sets, touch contamination, flush and hypochlorite treatment on the growth of biofilm in Tenckoff catheters discs. Peritoneal Dialysis Bulletin 7: S20, 1987 *Comment: using hypochlorite to prevent bacterial biofilm growth in catheters used for dialysis*

7) Wadhwa N.K. and others. Amuchina 5% vs. povidone iodine 10% solution for transfer set change in peritoneal dialysis patients. Peritoneal Dialysis International 17, S1, S46, 1997 *Comment: comparison of Amuchina vs. PI for the treatment of the skin around the exit site of PD Patients. Comparable results.*

8) Cabralda T., Wadhwa N.K. and others. Use of Amukin 50% solution vs. povidone iodine 10% solution for transfer set change in peritoneal dialysis patients. Advances in peritoneal Dialysis. Vol 14, 142-144, 1998. *Comment: comparison of Amuchina vs. PI in a high infection risk peritoneal dialysis procedure*

9) Grosman M and others. Amuchina in the prevention of the exit site infection (ESI) in children on chronic dialysis. Poster presented at XV International Congress of Nephrology, Buenos Aires, Argentina - May 1999 – *Comment: Amuchina vs. Chlorhexidine in treating the skin of young PD patients in Argentina. Same number of infections but less contraindication.*

10) Gaudet D. Antiseptic solutions for hemodialysis catheters. Canadian Association Nephrology Nurses & Technicians Journal 6, 4, 20-23, 1996 *Comment: review of the antiseptics available for the HD catheters. Includes Amuchina solutions.*

11) Clementi M. – Effect of a chlorine disinfectant on Hepatitis C Virus (HCV) in vitro: analysis of HCV binding to the cell surface receptors and analysis of viral replication. Acta Tox. Ther. XVIII, n.1, 25-31, 1997 *Comment: Virological test viable for HD disinfection of surfaces potentially contaminated by HCV*

12) Mishkin GJ and others – 10% electrolytic chloroxidizing agent (Exsept plus) to reduce infection rate in dialysis. American Journal of Kidney Diseases 39, no 4, April 2002 (A24) *Comment: comparative result analysis of two Dialysis Centers using PI or Exsept. Less infection in center using Exsept.*

December 20, 2002

VIA FACSIMILE AND REGULAR MAIL

John M. Taylor, III
Associate Commissioner for Regulatory Affairs
Food and Drug Administration
PKLN Bldg., rm. 1490 (HFC-1)
5600 Fishers Lane
Rockville, MD 20857

Re: Alcavis International, Inc. Citizen Petition - Docket No. 75N-183H Comment No. CP13

Dear Mr. Taylor:

This letter is an interim response to a letter from you dated November 14, 2002. In that letter, you stated that the Citizen Petition ("CP") filed by our company, Alcavis International, Inc., does not present information showing U.S. marketing history for sodium hypochlorite 0.10 to 0.50 percent as a patient preoperative skin preparation so as to be included in the Tentative Final Monograph ("TFM") for Over-the-Counter ("OTC") Healthcare Antiseptic Drug Products.[1]

We believe that FDA has prematurely and erroneously concluded that the CP did not present adequate U.S. marketing history to support the use of sodium hypochlorite 0.10 to 0.50 percent as a patient preoperative skin preparation and that the filing of a Time and Extent Application ("TEA") is inappropriate. Clearly, FDA's review was merely preliminary in that a closer look at the information and references in the CP provide the necessary evidence of the uses of this ingredient since World War I for site access or "cut-down" purposes. Such uses are a subset of what FDA later characterizes as preoperative skin preparation.

We are preparing a more detailed explanation of the information already contained in the CP and its references that addresses the use of sodium hypochlorite 0.10 to 0.50 percent as a patient preoperative skin preparation well before 1972. Due to my recent health related problems that resulted in surgery, our response to you has been slightly delayed and you should be expecting our correspondence within next few weeks.

[1] See, Federal Register of June 17, 1994, Vol. 59 p. 31402. (59 FR 31402).

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In the meantime, if you have any questions, please feel free to contact me.

Very truly yours,

Ludovico Giavotto/jsp

Ludovico Giavotto

cc: Dockets Management Branch
(Docket No. 75N-183H)