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August 22, 2003

US Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: [Docket No. 75N-183H]
RIN 0910-AA01

Dear Dr. Jackson:

Thank you for your previous communications and for permitting Cardinal Health, Medical Products and Services (Cardinal) to submit general comments concerning the "Tentative Final Monograph for Healthcare Antiseptic Drug Products; Proposed Rule, 6/17/94, for potential consideration.

1. Section 333.470 – Testing of healthcare antiseptic drug products
Subsections – a(1)(i)(ii)(iii)(iv)

Comment:

Concerning the number of microorganisms required, especially the clinical isolates, Cardinal believes that the testing number should be reduced to a total of 15 to 20 organisms. According to "The National Nosocomial Infections Surveillance (NNIS)" system for the incidence rate of pathogens from surgical site infections monitored over a six-year period (1990-1996), 87% of surgical site infections are caused by 13 microorganisms. Actually, the number of organisms is not the issue; rather it is the resistance of the specific organism to a specific antimicrobial agent that is of significance. The 13 microorganisms listed in the NNIS survey did not include MRSA, VRE, or VRSA, for example, which may be more resistant to certain chemical agents. With the most representative group of resistant organisms as bio-indicators, we only need to test the group of bio-indicators without having to worry about testing various pathogens. In addition, testing against 25 fresh clinical isolates and 25 ATCC laboratory strains is considered to be excessive.

2. Page 31432 – Federal Register/Vol. 59/No. 116/6-17-94

"However, any time-kill studies submitted to the Agency are to be conducted on a 10-fold dilution of the formulated product against the ATCC strains identified in Section 333.470(a)(1)(ii) of the proposed testing regulations and are to include enumeration at times at 0, 3, 6, 9, 12, 15, and 30 minutes."

75N-183H C66

Comment:

Cardinal believes that the "dilution factor" identified requires using a 1:10 dilution of antimicrobial product for testing purposes. During "real world" actual use scenarios, skin prep antimicrobial products do not experience dilution during their life cycles. Therefore, in vitro testing of antimicrobial products should not require 1:10 dilution of the antimicrobial. A 1:10 dilution of 70% alcohol will dilute an effective antimicrobial to a 7% alcohol solution, i.e., an ineffective antimicrobial solution. Continuing this thought, a 1:10 dilution of 4% CHG will produce 0.4% CHG. However, a 1:10 dilution of each antimicrobial solution will not reduce the antimicrobial effect of each solution by the same ratio. The alcohol solution will be reduced in effectiveness to a much greater extent than would be the CHG. Such a dilution requirement only serves to produce "false negatives" in our opinion. On the other hand, in terms of iodophor, a 1:10 dilution can accentuate the amount of free iodine thus improving antimicrobial efficacy, causing "false positives".

A "dilution factor", however, should be maintained concerning the testing of traditional hand scrub solutions where tap water rinsing is part of the procedure. For non-traditional hand scrub solutions, i.e., water-less scrub solutions, the "dilution factor" should once again be eliminated.

3. Page 31413 – Federal Register/Vol. 59/6-17-94

"The Agency has reviewed the marketing history of chlorhexidine gluconate and finds that although it has been marketed for professional or hospital use under NDA's, insufficient data remain in the public administrative record for this rulemaking to support general recognition of safety and effectiveness for OTC use. Accordingly, chlorhexidine gluconate 4 percent aqueous solution as a health-care antiseptic is a new drug and is not included in this tentative final monograph."

Comment:

It is the opinion of Cardinal that in the intervening nine plus years that have passed since the issuance of the Tentative Finial Monograph (6/17/94), a substantial period of time during which 4% CHG has continuously been used in both professional and hospital use as an antimicrobial agent, enough historical data, i.e., NDA annual reports, periodic NDA reports, Adverse Drug Reaction Reports (ADR), etc., are now available to the Agency to allow a recognition that 4% CHG should be considered a Category I (GRAS) compound which now should be included in the Final Rule which is being considered and, as such, should be permitted to be marketed in the United States without the requirement of NDA submission. For the same reason, 2% CHG should be similarly considered. CHG at this concentration is more safe and less toxic than 4% CHG.

4. Page 31445 – Section b – Effectiveness of a surgical handscurb
Subsection (iii)

"When tested, in vivo, by the test procedure for the evaluation of surgical handscurb products in paragraph (b)(1)(iii) of this section, reduces the number of bacteria 1-$\log_{10}$ on each hand within 1 minute and the bacterial cell count on each hand does not subsequently exceed the baseline within 6 hours on the first day, and produces a 2-$\log_{10}$ reduction of the microbial flora on each hand within 1 minute of product use by the end of the second day of enumeration, and a 3-$\log_{10}$ reduction of the microbial flora on each hand within 1 minute of product use by the end of the fifth day when compared to the established baseline."

Comment:

There is no reason to expect an active agent to perform differently, in log scale, on different days of testing. It is the opinion of Cardinal that the above-cited requirement be uniform at all testing times. The test requirement in the TFM appears to have been specifically designed for chlorhexidine gluconate (CHG), an NDA ingredient known for its ability to adhere to the stratum corneum and develop cumulative activity. CHG is the only compound, to our knowledge, capable of consistently passing this requirement. It is the opinion of Cardinal therefore that the requirement should be lowered.

5. General Comment:

A product, DurpPrep™, believed to have been marketed in the United States since 1988, to our knowledge without an NDA, uses a polyacrylate/iodine containing polymer as the active ingredient in the product. It is the opinion of Cardinal that polyacrylate/iodine containing polymers be categorized as Category I (GRAS) active ingredients and allowed to be marketed in the United States under the Final Monograph presently under consideration.

6. General Comment:

In our reading of the Tentative Final Monograph we do not see a specifically stated obligation requiring that all testing methods be validated. Such a required obligation may be implicit in the application of Good Laboratory Practice, however, in the interest of uniform test results and to account for the naïve tester, we believe that a validation requirement should be explicitly stated and where possible a validation method(s) should be identified.

The concept of validation should also be carried over to the area of neutralization. If the antimicrobial agent cannot be completely neutralized in a validated manner, efficacy-testing results can be biased. False positives may result from efficacy testing using non completely neutralized compounds especially when the active compound is formulated with a lotion, emollient, etc.

Attached is a copy of Chapter 25, "Testing Methodology of Preoperative Skin Preparation and Surgical Scrub as Over-the-Counter Drugs", by David K. Jeng, Sc.D., provided with the permission of the author, taken from the Handbook of Topical Antimicrobials, edited by Daryl S. Paulson (2003), to illustrate our position concerning the necessity of using validated testing methods and the proposal of using bio-indicators as testing organisms.

Once again Cardinal appreciates the opportunity to comment on the Monograph under review. Should clarification of additional information be required, please call me at 847-785-3310 or write to the above address or joe.merits@cardinal.com.

Regards,

Joseph A. Mertis

Joseph A. Mertis
Director, Regulatory Affairs
Cardinal Health