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07.03.2006

Re: Proposed Rule; Reopening of the Administrative Record for Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Health Care Antiseptic Drug Products. 68FR32003. Docket No. 75N-183H.

Dear Sir or Madam:

Please accept these comments in response to the Food and Drug Administration's (FDA) reopening of the administrative record regarding the tentative final monograph for Over-the-Counter (OTC) Health-Care Antiseptic Drug Products (FR 59(116):31402-31452, June 17, 1994) (1994 TFM). **These comments address suggested modifications of the TFM in regards to supportive testing, allowable labeling claims, and in the determination of an endpoint for different use patterns of the antimicrobial agents.**

SUMMARY:

The 1994 TFM prescribes the need for MIC testing and an assessment of effectiveness after both single and multiple washes. Additionally the TFM current limits the allowable antimicrobial activity claims.

We see no need for MIC testing nor the stipulation of multiple washes and differing requirements for efficacy after each wash. We submit that the assessment of efficacy should provide the same benefit for each patient and that every wash should meet the same criteria. Therefore an assessment after a single application is sufficient to determine the benefit of the antiseptic. In proposing testing of a single application immediate reduction log reductions have been proposed for both a Surgical Scrub and HealthCare Personnel Handwash. In regards to the limited antimicrobial activity claims allowed, the Health Care Workers of today's hospitals are in need of substantiation of activity against specific groups of microorganisms. We therefore prescribe that additional antimicrobial activity claims be allowed.

- **MIC tests are relevant for antibiotics but not for hand antiseptics.**
- **Single application efficacy assessments substantiate the same benefit for a patient and multiple wash assessments with different requirements are not necessary.**
- **A 2.7 log₁₀ reduction is prescribed for Surgical Scrubs and a 4.5 log₁₀ reduction for post contamination of hands.**

- Hospital workers are in need of knowledge of the general activity of the antiseptic against specific groups of microorganisms including (TB, fungi, viruses, spores).

DISCUSSION:

Aims for Modification of the TFM

1. No MIC tests

MIC tests are usually performed to determine if an isolate is susceptible or resistant to an antimicrobial agent. MIC tests are certainly relevant for antibiotics but their value for hand antiseptics is very limited. What does an MIC value really tell about a preparation which aim is to kill microorganisms? The relevance of an “inhibitory concentrations” appears to be clearly minor. Time-kill tests are from our point of view much more relevant for hand antiseptics.

2. Allow label claims for different types of antimicrobial activity

Based on the most comprehensive review on the epidemiologic evidence for hand hygiene it has been suggest that preparations should have at least bactericidal, fungicidal (yeasts), and virucidal (enveloped viruses) activity [1]. Health care workers in hospitals often need to know whether a general activity against a specific group of microorganisms is given by the preparation used for hand antiseptics. The antimicrobial activity is typically classified in:

- bactericidal,
- tuberculocidal,
- fungicidal (yeasts),
- fungicidal (all fungi),
- virucidal (enveloped viruses),
- virucidal (all viruses), and
- sporocidal.

This type of information on the label in combination with the appropriate killing-time or inactivation-time (viruses) would be a helpful information for the health-care personal and clarify an appropriate use of different formulations (e.g. if the application time is beyond the typical clinical use of a preparation which is normally 30 sec). The need for such label claims has recently also been emphasized by Professor Sattar [2].

3. Assessment of a single application

The current test methods describe a repetitive use of a preparation which has several significant limitations regarding the conclusion in clinical practice:

- a. The observed efficacy is only realistic in the specific pattern of application which is described in the TFM (e.g. eleven applications in 5 days). Any change of the application pattern does not allow to determine the efficacy anymore.
- b. The efficacy of chlorhexidine salts may be significantly reduced by various agents which neutralize the antimicrobial efficacy in clinical practice. One example is the use of a liquid soap or a cream containing anionic detergents [3]. As this can not be predicted in real life the specific pattern of use in the TFM bears significant hazards.
- c. The endpoints for surgical scrubs are currently variable with a lower requirement after the 1st application and a higher threefold requirement after the 11th application. This is from our point of view not ethical as every single treatment should reveal the same efficacy and thereby the same benefit for a patient. That is why we prefer the assessment of the efficacy of a single application.

4. Specify new endpoints (not significantly less effective than reference procedure):
 - a. Surgical scrub: immediate effect of 2.7 log₁₀ reduction
 - b. Post contamination treatment of hands: immediate effect of 4.5 log₁₀ reduction

Based on the scientific literature evidence-based endpoints can be recommended for the efficacy which were derived from standard treatments. It has been shown that the reference surgical hand disinfection can reduce the bacterial density on hands on average by 2.7 log₁₀-steps [4]. This would certainly be a higher but reasonable requirement compared to the current TFM. A reference treatment for the post-contamination treatment of hands has been described to reduce the bacterial density on artificially contaminated hands on average by 4.5 log₁₀-steps [5, 6]. We consider this to be a reasonable and evidence-based approach to define efficacy standards and requirements.

CONCLUSION

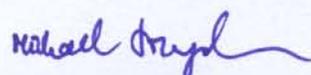
We respectfully request that FDA take our “Aims for Modification of the TFM” under consideration in their continued work in proceeding towards the finalization of the Monograph for HealthCare Antiseptic Drug Products.

We have listed below the references used in obtaining these aims and conclusions. A copy of each is attached for your perusal.

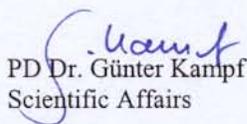
Thank you again for your consideration.

Sincerely

BODE Chemie GmbH & Co.



Dr. Michael Stengele
Regulatory Affairs / Documentation



PD Dr. Günter Kampf
Scientific Affairs

References

1. Kampf G, Kramer A: **Epidemiologic background of hand hygiene and evaluation of the most important agents for scrubs and rubs.** *Clin Microbiol Rev* 2004, **17**(4):863-893.
2. Sattar SA, Springthorpe VS, Tetro J, Vashon R, Keswick B: **Hygienic hand antiseptics: should they not have activity and label claims against viruses?** *Am J Infect Control* 2002, **30**(6):355-372.
3. Benson L, Bush L, LeBlanc D: **Importance of neutralizers in the stripping fluid in a simulated healthcare personnel handwash.** *Infect Control Hosp Epidemiol* 1990, **11**(11):595-599.
4. Kampf G, Ostermeyer C: **Influence of applied volume on efficacy of 3-minute surgical reference disinfection method prEN 12791.** *Appl Environ Microbiol* 2004, **70**(12):7066-7069.
5. Kampf G, Ostermeyer C: **Inter-laboratory reproducibility of the EN 1500 reference hand disinfection.** *J Hosp Infect* 2003, **53**(4):304-306.
6. Kampf G, Ostermeyer C: **Intra-laboratory reproducibility of the hand hygiene reference procedures of EN 1499 (hygienic hand wash) and EN 1500 (hygienic hand disinfection).** *J Hosp Infect* 2002, **52**(3):219-224.