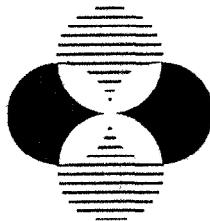


**CREM**  
Centre for Research on  
Environmental Microbiology  
(613) 562-5800 ext 8313/4 phone  
(613) 562-5452 fax  
crem@uottawa.ca email



**CRME**  
Centre de recherche en  
microbiologie environnementale  
tél. (613) 562-5800 ext 8313/4  
télééc. (613) 562-5452  
email: crem@uottawa.ca

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**BY FAX**  
**(301-443-3100)**

June 22, 2004

Lester M. Crawford, DVM, PhD  
Acting Commissioner  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857  
U.S.A.

Dear Dr. Crawford:

**Re: FDA document entitled *Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products (21 CFR Parts 333 and 369); Docket No. 75N-183H***

I am taking the liberty of writing to you as a concerned researcher who has devoted the better part of his scientific career investigating the role of microbicides in the control of infectious agents. My concern is the above-mentioned rule-making which has been under development and discussion for almost 26 years now. Its latest version is dated July 17, 1994.

This letter concerns (1) difficulties with the testing requirements as specified in the Tentative Final Monograph (TFM); (2) the failure of the monograph to address viruses; and (3) the failure of the Agency to respond in a timely and productive manner.

While one of the objectives of the TFM is to provide guidance to industry on the testing of topicals, I believe that its promulgation as currently written is likely to achieve the reverse because the entire document is written with *antibiotics* in mind. In its current form it has very little relevance to topicals. As a result, the testing requirements specified in it are just too onerous and downright unreasonable. For example, it requires the testing of each formulation against over 50 (25 lab and 25 clinical) strains of each of 19 separate species of bacteria and several more strains of a non-filamentous fungus. The required determinations of the minimal inhibitory concentrations (MIC) and time-kill would easily amount to over one thousand individual tests. Initial estimates indicate that such testing may cost as much as three million dollars for each product. Even large multi-nationals may not be able to justify making an investment of this magnitude. Besides, there is no good scientific justification for the extensive testing. In the case of

**75N-183H**  
Faculty of Medicine, University of Ottawa  
451 Smyth Road, Ottawa, Ontario  
K1H 8M5 Canada

**C90**  
Faculté de médecine, Université d'Ottawa  
451 chemin Smyth, Ottawa, Ontario  
K1H 8M5 Canada

antibiotics, the risk from failure can be high, thus necessitating a higher level of stringency in efficacy testing. Topicals are marketed for neither injection nor ingestion, but rather to be applied on intact skin or mucous membranes. Therefore, the testing requirements for topicals should not be nearly as stringent as those for antibiotics.

This proposed rule-making also totally ignores the practical difficulties of complying with some of its requirements. For example:

1. It is virtually impossible to find 25 lab strains of many types of bacteria listed in the TFM. Even the American Type Culture Collection (ATCC), the most extensive of its kind in the world, does not list those many strains.
2. Clinical strains are an even bigger problem because:
  - a. most contract laboratories, which normally perform microbicidal testing for manufacturers, simply do not have ready access to the large numbers of clinical strains required; even if such strains were available at local hospitals or clinical laboratories, meeting the regular demand from contract laboratories would create an unreasonable burden on their resources;
  - b. in the current climate, there are also mounting restrictions on the shipment of infectious materials;
  - c. clinical isolates are generally not as well characterized as standard laboratory strains; this could be a significant source of variability in the test data;
  - d. fresh clinical isolates often do not grow to high enough titers necessary for microbicidal testing; and
  - e. clinical isolates cannot be passaged more than once or twice before they turn into lab-adapted strains.
3. The microbicidal potential of the active ingredient is to be tested on its own. This is often difficult because many such chemicals are not readily water soluble and require other additives to formulate properly. Even if the active could be tested on its own, the data generated would be of questionable value since excipients add value to a given formulation.
4. MIC values for topicals are to be determined with procedures commonly used for antibiotics, which present several problems:
  - a. such procedures are inherently unsuitable for working with microbicides because any culture medium to be used in testing will neutralize much of the microbicidal activity right at the outset;
  - b. The end-point in broth-based tests is the absence of turbidity in the culture tube; many test formulations add their own turbidity to the culture medium thus making the interpretation of the data difficult.

5. In *in vivo* tests for pre-operative skin preparations over 70% of the subjects fail to meet the TFM's required 3 log<sub>10</sub> baseline entrance criterion on abdominal sites.
6. The National Committee for Clinical Laboratory Standards (NCCLS) and the standards of ASTM International referenced in the TFM are now dated and should be replaced with the current versions of ASTM standards.

The TFM also makes no mention of viruses and testing against them. As you may know, many viruses can survive well on human hands and epidemiological evidence strongly suggests their handborne spread. Standardized methods and safe and suitable surrogates are now available for testing the virus-eliminating activity of topicals. A Citizens Petition on this subject was submitted in January 2003 to the FDA from a large industry coalition. It details the scientific rationales for testing against viruses and provides recommendations on test methodology and surrogates viruses. The Agency has not yet responded to it.

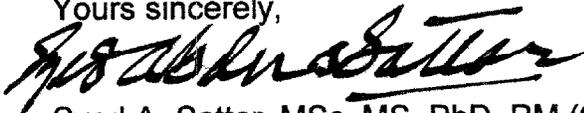
FDA is a recognized world leader in regulation of foods, drugs and medical devices. It is, therefore, incumbent on such as an organization to issue regulations that are not only scientifically sound, but also in tune with market realities. I believe that the TFM has the potential to undermine the competitiveness of the U.S. industry while discouraging research and innovation in the field of topical antimicrobial products.

The delays in its finalization have also rendered certain crucial parts of the monograph already out of date. This is particularly true for the methods listed in it for generating the required test data.

Concerns with the TFM have been discussed before in national forums and workshops and in meetings with representatives of the FDA. However, so far there are no indications that public input is being given due consideration by the Agency. Through this letter, I would request you look into the matter at your earliest convenience.

Please let me know if you need more information in the matter. I would also appreciate knowing the receipt of this letter.

Yours sincerely,



Syed A. Sattar, MSc, MS, PhD, RM (CCM), FAAM  
Director, CREM

- c.c. - Charles J. Ganley (HFD-560)  
- Debbie Lumpkins (HFD-560)  
- Peter Coderre (HFD-520)  
- Dockets Management Branch (HFA-305)