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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

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

Dear Sir or Madam:

The Soap and Detergent Association and The Cosmetic, Toiletry, and Fragrance Association (Industry Coalition) hereby submit the following comments to the above-referenced rulemaking. The Industry Coalition views the reopening of the administrative record by the Food and Drug Administration (FDA) to admit additional data and to provide an opportunity for comment as a laudable step that clearly recognizes the pivotal role of the data in informing FDA's determinations of safety and efficacy. The Industry Coalition commends the FDA on this initiative. However, research by companies on various ingredients and testing criteria relevant to this monograph is ongoing, and we therefore urge the Agency to continue to exercise discretion by permitting new data and information to be submitted to the record beyond August 27, 2003 to ensure that the rulemaking record is as complete as reasonably possible prior to issuance of the final monograph (FM). In particular, the Industry Coalition seeks assurance that all data and research relevant to both professional and consumer antiseptic products will be considered by the Agency within the scope of this rulemaking.

These comments address specifically the need, and the underlying legal and policy considerations, for FDA to accept new data and information on active ingredients beyond the deadline cited, and, if necessary and appropriate, to defer final actions on active ingredients which are the subjects of ongoing research and/or dependent on agency feedback, even after a Final Monograph is adopted.

I. Background

75N-0183H C79

On May 29, 2003, FDA published a proposed rule announcing the reopening of the administrative record for the Topical Antimicrobial Drug Products for Over-the-Counter (OTC) Human Use. 68 Fed. Reg. 32003 (May 29, 2003) (the "May 29 notice"). The notice pertained specifically to the rulemaking for health care antiseptic products that was published on June 17, 1994. 59 Fed. Reg. 31402.

CTFA is the national trade association representing the cosmetic, toiletry and fragrance industry. Founded in 1894, CTFA has an active membership of approximately 300 companies that manufacture or distribute the vast majority of finished personal care products marketed in the United States. CTFA also includes approximately 300 associate member companies, including manufacturers of raw materials, trade and consumer magazines, and other related industries.

The Soap and Detergent Association is the non-profit trade association representing some 120 North American manufacturers of household, industrial and institutional cleaning products; their ingredients; and finished packaging. SDA members produce more than 90% of the cleaning products marketed in the U.S.

In the notice, FDA stated that, although the administrative record for this TFM had officially closed on August 17, 1995, the agency was nonetheless reopening the administrative record to accept data and information submitted after that date for consideration in the FM and to permit interested persons to submit comments on the data and information. The notice stated:

> Under § 330.10(a)(7)(v), new data and information submitted after August 17, 1995, prior to the establishment of a final monograph (FM), are considered a petition to amend the monograph and are to be considered only after a FM has been published unless the agency finds that good cause has been shown that warrants earlier consideration. Further, under § 330.10(a)(10)(ii), the agency shall make all decisions and issue all orders under § 330.10 in the FM solely on the basis of the administrative record and shall not consider data or information not included as part of the administrative record.

68 Fed. Reg. at 32004 (emphasis added).

Pursuant to the underscored exception, FDA stated that it was treating as petitions to reopen the administrative record all new data and information submitted after August 17, 1995, some of which related to proposed Category II and Category III ingredients, and was granting those petitions to reopen. "Because these data are relevant to the final classification of these ingredients and to the testing criteria to be established in the FM, FDA has determined that good cause exists to consider these new data and information in developing the FM for these products." Id. The agency further stated that it will continue to receive new data submissions and comments until August 27, 2003, after which the administrative record for this rulemaking will be closed.

For the reasons discussed below, the Industry Coalition urges that FDA continue to accept new data on specific ingredients and testing criteria for consideration in the professional health care antiseptic products FM beyond August 27, 2003. Our request is of significant importance given the Agency's intention to complete this rulemaking in stages. If FDA finalizes the professional healthcare products rulemaking first, it must provide some type of process for the public to contribute additional data and information that is relevant to the record for other categories of topical antimicrobial products, *e.g.*, consumer and foodhandler[1]. In addition (or alternatively, if FDA will not accept data beyond this deadline), we request that FDA, at the very least, defer final action on those Category II and III ingredients for which substantive studies or research are ongoing or dependent upon Agency feedback. Allowing such further submissions is consistent with the law, FDA's regulations and policies, and the facts relating to the Topical Antimicrobial Rulemaking, and is in the best interests of the consumer.

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[1]We assume that FDA will propose regulations on foodhandler products as well, although no specific timetable has been announced.

II. FDA Should Continue To Accept New Data And Information Into The Administrative Record For The Health Care Antiseptic FM Beyond August 27, 2003

From its inception, the Topical Antimicrobial Rulemaking has been a particularly complex and cumbersome proceeding. The Topical Antimicrobial Rulemaking was actually the second proposed monograph in the OTC Drug Review, first issued in 1974, then re-issued in 1978. Yet the proceeding is still ongoing to this day and is apparently destined to be among the last monographs to be finalized.

In connection with the rulemaking on health care antiseptic products, significant technical, scientific and practical issues have led to development of initiatives such as the Health Care Continuum Model, a model proposed by the Industry Coalition in 1995 that was intended to address the benefits and risks of the different uses of these ingredients.

As the agency recognizes, the current health care antiseptic rulemaking is one of substantial importance for health care professionals and consumers alike. A "health care antiseptic" product is defined as "an antiseptic containing drug product applied topically to the skin to help prevent infection or to help prevent cross contamination." 59 Fed. Reg. at 31442 (proposed § 333.403(c)). This category includes a broad range of well-known ingredients with a relatively long history of safe and effective use in medical, food handler and consumer settings. FDA's regulation of the category thus has significant implications for public health. Recent health issues such as SARS, the potential for deliberate acts of bioterrorism, food safety initiatives and the need for urgent and proper care and products in such situations, illustrate the importance of these products to public health.

Given the complexity of many issues that have surfaced over the years in this rulemaking, FDA should continue to exercise maximum latitude in allowing manufacturers to submit relevant safety, efficacy and other data on ingredients and testing criteria to the administrative record prior to issuance of the FM. Moreover, there are sound equitable and policy reasons for FDA to exercise its discretion to enhance and enlarge the administrative record in this respect.

A. Continued Acceptance of Data Beyond August 27, 2003 Would Ensure That Manufacturers' Due Process Rights Are Adequately Protected

FDA has long since recognized the importance of manufacturers' stake in the OTC Drug Review, and has acknowledged the corresponding principles of fairness and due process upon which the Review is based. In rejecting a comment in 1972 that the TFM step be omitted from the process, FDA reasoned: "The procedures provided in the [OTC] regulations are designed to assure that all interested persons have an opportunity to have their comments reviewed by the Commissioner prior to the publication of the final monograph. The Commissioner recognizes that this review vitally affects the interests of the public and of manufacturers and that procedural fairness is essential to guaranteeing substantive fairness." 37 Fed. Reg. 9464, 9471 (May 11, 1972) (final rule on OTC drug classification procedures). Accord 46 Fed. Reg. 47730 (Sept. 29, 1981) (final rule on revision of procedures relating to Category III) ("[t]he procedures provided in the OTC drug review regulations . . . are designed to assure that all interested

persons have an opportunity to express their views at each stage of the process and to have their comments and objections reviewed by the agency before the publication of a final monograph").

Here, pursuant to its regulations, the agency has provided 90 days' notice to submit and/or to comment on data and information. However, given that such data and information have major implications for a broad range of companies, health care professionals and consumers, the Industry Coalition urges FDA to continue to accept data beyond the deadline. If data and information are refused admission to the administrative record because they are submitted after the deadline, not only will manufacturers be denied the valuable opportunity to obtain a timely evaluation of their data, but health care professionals and consumers will be deprived of much-needed safe and effective OTC medications. Given the magnitude of the interests at stake, the notice provided for completion of ongoing studies of health care antiseptic ingredients is insufficient to afford adequate protection to manufacturers of their due process rights.

Moreover, FDA's definition of "good cause" compels this result. In this situation, the comment period on the amended TFM closed on August 17, 1995. The data and comments submitted after that date have been treated as petitions to reopen the administrative record and have been admitted to the record, pursuant to FDA's regulation, 21 C.F.R. § 330.10(a)(7)(v). As noted above, FDA has determined that "good cause" exists to admit into the record new data and information submitted after August 17, 1995 because "these data are relevant to the final classification of these ingredients and to the testing criteria to be established in the FM." 68 Fed. Reg. at 32004. However, the same can potentially be said of new data and information that will become available after August 27, 2003. If these data pertain to ingredients classified in the rulemaking in Categories II and III or to testing criteria to be established in the FM, they are no less "relevant" than the data submitted between August 17, 1995 and August 27, 2003, and should likewise be treated as petitions to reopen the record and admitted to the record for "good cause." [2]

Therefore, FDA should apply this standard of good cause consistently to admit <u>all</u> data determined to be "relevant," including any such data submitted to the agency after August 27, 2003.

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[2] Indeed, it is noteworthy that several manufacturers of active ingredients that submitted data to support Safety and Efficacy after the docket was last closed in 1995 are still waiting for feedback from the Agency. Unless the Agency provides a workable mechanism to submit additional data after August 27, 2003, these same manufacturers will be required to submit supplemental citizen petitions to update their previously filed citizen petitions, as they continue to wait for clarification of the Agency's requirements for demonstrations of safety and effectiveness.

B. Failure Of FDA To Exercise Flexibility With Regard To The August 27, 2003 Deadline Would Undermine The Policy Objectives Of The OTC Drug Review

Rigid adherence by FDA to the August 27, 2003 deadline at this point in the process would fundamentally undermine the policy objectives of the OTC Drug Review. In the preambles to the 1972 rulemaking on OTC drug classification procedures, FDA emphasized the benefits of administrative rulemaking as a means of establishing the safety and effectiveness of OTC drugs over a case-by-case enforcement approach with respect to each potentially violative product under the new drug provisions. 21 U.S.C. §§ 321(p) and 355. FDA cited limited agency funding and manpower, the inefficiency of and burden on both the agency and courts in addressing violative products on an individual basis, and the resulting inadequate consumer protection and competitive unfairness if enforcement were directed to certain violative products while similar competitive products were permitted to remain on the market. See 37 Fed. Reg. 85, 86 (Jan. 5, 1972) (proposed rulemaking for OTC drug classification procedures). FDA then (and now) viewed the OTC Drug Review process as the most efficient, expeditious and fair means of assuring the safety and effectiveness of marketed OTC drug products. The agency declared:

> The Food and Drug Administration believes that its resources of manpower and funds are properly considered in deciding how best to approach its consumer protection activities. Based on present resources, it would not be possible to adopt a drug-by-drug approach even if it were a better method. The Commissioner has also concluded that a drug-by-drug approach is not the best method of proceeding, since it would be so cumbersome, time consuming, and confusing. By adopting these regulations there will be no question as to which drugs are generally recognized as safe and effective and not misbranded, and what labeling is permitted. Competitive unfairness alone would not sway the Food and Drug Administration from acting on a drug-by-drug basis where necessary to protect the public, but, if the Food and Drug Administration were to proceed against one product and remove it from the market, a competitive product that is no safer or no more effective would still be available to the consumer. Under these circumstances, selective enforcement serves no useful public purpose, and agency resources are more efficiently spent doing the complete job rather than a small part of it.

37 Fed. Reg. 9464, 9465 (May 11, 1972) (final rule on OTC drug classification procedures).

To accommodate these various goals, FDA has traditionally incorporated a large degree of flexibility into the OTC Drug Review, and has reiterated the need for such flexibility on numerous occasions in the context of the Review. For example, in response to a comment requesting the agency to designate the order of review of various therapeutic categories, to enable interested persons to prioritize data collection in an expeditious manner, FDA stated: "This comment has merit, but the Commissioner is unable at this time to give the order in which these categories will be reviewed. This information will be made public as soon as it is

available. It will, however, also be necessary to keep some flexibility in the system in the event that circumstances later require rearranging the tentative schedule." Id. at 9472.

Similarly, FDA declined to adopt a comment that time limits should be placed on the panels' deliberation and due dates for reports so that that review would be completed within a definite time frame, stating: "The amount of data submitted may vary by drug category. It is therefore inappropriate to set down a time limit within which the review must be completed. For this reason no time limit will be set even though the Food and Drug Administration wishes to expedite the panels' consideration as much as possible." Id. at 9466.

It is clear that FDA has consistently recognized the importance of conducting and completing the OTC Drug Review in a comprehensive, thorough, accurate and fair manner, and has exercised its discretion accordingly. With respect to the TFM at issue, it would be shortsighted of FDA to unbendingly enforce its August 27 deadline.[3]

Although FDA's regulations provide that new data submitted after the administrative record closes may be considered through the citizen petition process, 21 C.F.R. § 330.10(a)(12), this route presents a significant disadvantage in that it necessitates a case-by-case review by FDA. From the practical standpoint of conserving agency resources, such individual review via the citizen petition process fails to differ substantially from the case-by-case enforcement approach that the OTC Drug Review was designed to avoid. Moreover, while review of the citizen petition should be based on the data submitted in the petition, much of the future data would relate to studies that have already been submitted to this administrative record, and would have to be assessed in the context of such previously submitted data. Consideration of data in the context of the rulemaking has the added advantage of providing for an "open dialogue" between and among the various interested parties and FDA and ensuring that the scientific record in complete. Furthermore, the need for de novo judicial review might well arise if an OTC product failed to meet the conditions of the FM because the product's manufacturer was not permitted to introduce its data into the record, the manufacturer continued to market its product after publication of the FM on the basis of new data confirming the safety and effectiveness of its product, and either (1) the manufacturer sought a declaratory judgment that its product is generally recognized as safe and effective, or (2) FDA were to take enforcement action against the marketed product. FDA itself has conceded that such de novo review would be patently out of line with one of the fundamental goals of the OTC Drug Review: "While the comment is correct that issues not before the agency in an administrative proceeding may be litigated in court, such de novo judicial review is time consuming and wasteful. Avoiding such litigation was one of the reasons for establishing the OTC Drug Review as a rulemaking proceeding." 46 Fed. Reg. at 47738 (responding to comment arguing that if new data became available after FDA closed the rulemaking record, FDA's FM would not be controlling with respect to the new data; rather, de novo judicial review of the data would be warranted under Citizens to Preserve Overton Park v. Volpe, 401 U.S. 402, 415 (1971)).

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[3] Indeed, FDA has generally been flexible in the past in this very TFM. See 47 Fed. Reg. 39406 (Sept. 7, 1982); 47 Fed. Reg. 22324 (May 21, 1982); 47 Fed. Reg. 436 (Jan. 5, 1982); 45 Fed. Reg. 18398 (Mar. 21, 1980); 44 Fed. Reg. (Oct. 26, 1979); 44 Fed. Reg. (Mar. 9, 1979) (notices advising of reopening of administrative record). There is no compelling reason not to continue that policy.

A case-by-case approach – whether through a citizen petition or in connection with individual enforcement actions – would be a monumental waste of agency resources (particularly if numerous citizen petitions are submitted) and would defeat one of the primary goals underlying the establishment of the OTC Drug Review. As FDA itself recognized back in 1972 – and we agree – the "agency's resources are more efficiently spent doing the complete job rather than a ... part of it." 37 Fed. Reg. at 9465. The more sensible approach would be for FDA to be flexible with respect to the acceptance of new data submissions on ingredients and testing criteria for the FM.

III. In Addition, FDA Should Defer Final Action On Certain Ingredients When The FM Issues

In addition, (or in the alternative, if FDA will not accept data beyond the August 27, 2003 deadline), FDA should at least be prepared to defer from the FM those ingredients that have been tentatively established in Categories II and III and for which substantive studies are ongoing or dependent upon agency feedback. Deferral of final action with respect to certain ingredients would expedite the rulemaking process for the bulk of the relevant ingredients while permitting the agency to continue to receive and evaluate data on the deferred ingredients. This would benefit health care professionals and consumers, as the status of more marketed safe and effective products would be settled over time.

There is ample precedent for deferral of final action on ingredients in the OTC Drug Review after an FM has been issued. FDA has followed that practice in several FMs, including the following:

- Anorectal Drug Products, 55 Fed. Reg. 31776 (Aug. 3, 1990) (deferring final action on hydrocortisone and live yeast cell derivative pending a full review of the data);

- Topical Acne Products, 56 Fed. Reg. 41008 (Aug. 16, 1991) (deferring final action on benzoyl peroxide by publishing a separate, amended TFM for acne products containing benzoyl peroxide (56 Fed. Reg. 37622 (Aug. 7, 1991));

- Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products; Antihistamine Products; 57 Fed. Reg. 58356, 58357 (Dec. 9, 1992) (deferring final action on doxylamine succinate in light of new study submitted to administrative record for TFM suggesting potential carcinogenicity in animals);

- Digestive Aid Drug Products, 58 Fed. Reg. 54450 (Oct. 21, 1993) (deferring final action on lactase enzyme pending full review of the data);

- Boil Treatment Products, 58 Fed. Reg. 60332, 60332-33 (Nov. 15, 1993) (deferring final action on benzocaine to External Analgesic rulemaking);

- Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products; Antitussive Drug Products; 59 Fed. Reg. 29172, 29173 (June 3, 1994) (deferring issue of "multiuse" labeling (i.e., labeling for some or all of the proven pharmacologic activities of a drug, whether or not the conditions to be treated are related) to future amendment);

- Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products; Nasal Decongestant Products; 59 Fed. Reg. 43386 (Aug. 23, 1994) (deferring final action on phenylpropanolamine pending resolution of safety issues);

- Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products; Products Containing Diphenhydramine Citrate or Diphenhydramine Hydrochloride; Enforcement Policy; 61 Fed. Reg. 15700, 15702 (deferring final action on use of menthol for treating concurrent symptoms in either single-ingredient or combination drug products);

- Sunscreen Drug Products, 64 Fed. Reg. 27666, 27670 (May 21, 1999) (deferring final action on two sunscreen ingredients due to the lack of compendial monographs); and

- Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products; Combination Drug Products; 67 Fed. Reg. 78158, 78159 (Dec. 23, 2002) (deferring final action on use of promethazine combinations pending a full review of the data).

It is apparent from this list that several important ingredients have been deferred from final action and have been permitted to remain on the market until additional data have been generated and submitted in order to resolve pending safety or efficacy questions.[4] By its very nature, the OTC Drug Review is a "staged," or segmented, process. As with other rulemaking proceedings of such significant breadth or scope that simultaneous issuance of all final regulations is of dubious feasibility, the regulations within the OTC Drug Review have necessarily been implemented in stages. FDA's decision in the above examples to defer final approval of certain ingredients while finalizing the FM for others is in accordance with the general staged approach that is characteristic of the OTC Drug Review. Such an approach makes good sense when considering the policy objectives of the Review to expedite determinations of safety and effectiveness, while at the same time ensuring adequate opportunity for submission by interested parties and thorough review by FDA of the pertinent data and information.

[4] Permitting the continued marketing of such products pending a final determination of ingredients' status is consistent with Cutler v. Kennedy, where the court clearly recognized FDA's discretion to not seek enforcement action with respect to marketed products containing Category III ingredients. 475 F. Supp. 838, 856 (D.D.C. 1979).

The Industry Coalition therefore urges FDA to defer final action on those Category II and III ingredients whose safety and effectiveness are currently being studied, and to permit the continued marketing of those ingredients in already marketed OTC drug products pending a final determination of the ingredients' status.

IV. Conclusion

In closing, the Industry Coalition applauds FDA for reopening the administrative record in this rulemaking to formally admit important new data and information on ingredients and testing criteria for consideration in developing the FM. This is an important step in the recognition that there is significant ongoing research that is directly relevant to the Agency's evaluation of the safety and efficacy of these ingredients for topical antimicrobial use. It is a dynamic area in terms of research regarding testing methodology through the American Society for Testing and Materials[5] and antimicrobial resistance, for example. The evolving standards in this area make it all the more critical that FDA continue to admit data relevant to the safety and efficacy of health care antiseptic products. Ultimately, it is the consuming public that stands to benefit from the careful consideration of all relevant data substantiating the safety and efficacy of these products.

For these reasons, the Industry Coalition requests that FDA (1) continue to accept into the administrative record data and information relevant to the safety and effectiveness of Category II and III ingredients and to testing methods to be established in the FM, and (2) to defer final action on ingredients where substantive testing is ongoing or dependent on agency feedback and no significant safety concerns exist.

Sincerely,

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Richard I. Sedlak
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cc: Charles J. Ganley, M.D. (HFG-560)
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[5] See e.g., comments of the Industry Coalition on the TFM and the proposal of the Healthcare Continuum Model (June 15, 1995), a detailed proposal on finished product testing methodology (September 29, 1999), and a Citizen Petition on surrogate endpoint test methods (November 28, 2001). We have been advised by FDA that it is not necessary to resubmit these and other documents filed by the Industry Coalition since the rulemaking record closed.