II. Combinations

II. Comments in Support of FDA's Position on OTC Combinations of Antigingivitis/ Antiplaque Ingredients with other GRAS/E Oral Care Ingredients

The Subcommittee recommended that certain OTC ingredients reviewed in other OTC Review rulemakings but not the antigingivitis/antiplaque rulemaking be permitted to be combined with the proposed GRAS/E antigingivitis/antiplaque ingredients (i.e., CPC, SnF and EOM). Specifically, the Subcommittee stated:

> "E. Combination Drug Products
> "1. General Combination Policy: The Subcommittee recognizes that there may be a reason for combining active ingredients in certain OTC drug products. However, such combinations must be based on a sound and logical scientific rationale. The Subcommittee applied the OTC drug review regulation in Sec. 330.10(a)(4)(iv) in developing a combination policy for antigingivitis/antiplaque drug products. The Subcommittee believes that it is rational to combine oral health care ingredients that meet the regulatory requirements as well as the criteria adopted by the Subcommittee, together with suitable inactive ingredients, provided that: (a) Each active ingredient makes a contribution to the claimed effect, (b) the active ingredients are safe and effective and combining the ingredients does not decrease the effectiveness of any individual ingredient, (c) combining the ingredients does not decrease the safety of the combination
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> compared to a single ingredient, (d) the inactive ingredients are safe and do not interact with or otherwise inhibit the effectiveness of the active ingredients, (e) there is a significant target population that can benefit from the use of the combination, and (f) the combination contains adequate directions for use and is labeled with adequate warnings against unsafe use.
> "The Subcommittee concludes that the same general principles apply when an active ingredient from a different pharmacological class reviewed by another OTC drug advisory panel is combined with an active ingredient reviewed by this Subcommittee. The rationale for such combinations should be evaluated by FDA according to the combination policy set forth in the reports of both advisory panels and in accordance with the agency's regulations." (emphasis added)

The OTC Combination Policy cited above by the Subcommittee is found in 21CFR 330.10(iv), as follows:

> "(iv) An OTC drug may combine two or more **safe** and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the **safety** or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational

> concurrent therapy for a significant proportion of the target population." (emphasis added)

We note that FDA dissented from the Subcommittee's position stating that the Subcommittee was only asked for its general recommendations, and that the agency is not aware of any marketing history of such combinations eligible for the OTC drug Review nor were such combinations were submitted for review.[a]

While we generally favor the broad availability of rational safe and effective single ingredient and combination OTC ingredients under the OTC Review, our position is nonetheless necessarily framed within the context of the existing applicable regulations. Under the regulatory foundational underpinnings of the OTC Review cited in 21CFR 330.10a(4)(i), safety is defined as:

> "(i) Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data." [21CFR330.10a(4)(i)] (emphasis added)

Thus, we conclude that to be consistent with the existing regulations, including the recently promulgated material time and extent rule, there has been an insufficient showing of evidence in the Subcommittee's report (i.e., the ANPR) for the proposed combinations to be permitted at this time in the OTC antigingivitis/antiplaque rulemaking as "Category I GRAS/E" combinations I. The absence of data and the sole argument that the combinations are "rational" per FDA's combination policy does not meet the safety standard in the definition of safety under the OTC Review, which is required under the same combination policy cited by the Subcommittee. [21CFR 330.10a(4)(iv)]

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[a] [68FR32232]: "The Subcommittee was asked for its general recommendations on combination products in which antigingivitis/antiplaque ingredients are combined with other oral health care ingredients. The Subcommittee recommended the following as rational oral health care combination products: (1) An antigingivitis/antiplaque active ingredient combined with an anticaries active ingredient, (2) an antigingivitis/antiplaque active ingredient combined with a tooth desensitizer active ingredient, and (3) an antigingivitis/antiplaque active ingredient combined with an anticaries active ingredient and a tooth desensitizer active ingredient.
"However, the agency is not aware of any marketing history of such combination products eligible for the OTC drug review, nor were such combinations submitted to the Subcommittee. Therefore, the agency is dissenting from these recommendations at this time. Data are needed to establish the safety and effectiveness of these combination products. Accordingly, none of the combination products described above may be marketed OTC at this time under this advance notice of proposed rulemaking. The agency invites supporting data and information demonstrating that these combination products can be generally recognized as safe and effective for OTC use."

Since "safety" is a key criterion of the combination policy and specifically includes by definition "significant human experience during marketing" 21CFR330.10a(4)(i), it can only be concluded that combination products have to be "submitted" to the rulemaking *in the context of their intended use for comprehensive review of their safety and "significant human experience during marketing."* Such combination products could not qualify for potential monograph status if they were submitted with data used to support only one ingredient in their combination. In other words, if a fluoride-CPC product were submitted for a comprehensive safety review by the Subcommittee, then the safety and effectiveness assessment would be in the context of its dual intended use, and not just its antigingivitis/antiplaque intended use, to be sure for example that the conditions of use of the second indications (anticaries use) did not affect its safety and effectiveness. We are unaware at this time that such a review was undertaken for any one of the combinations recommended by the Subcommittee, and therefore we concur at this time with FDA's position, based on our understanding of the available data.