

Alternative Dose Forms

5.B. The monograph should allow for alternate topical oral dose forms in order to provide for maximum marketing flexibility (§356.13 and §356.15)

The intent of the OTC Monograph system is to establish a thorough review of the *active ingredients* utilized in OTC drug products, as opposed to a review of finished drug products that are approved via NDAs. This long-standing Agency position was reviewed in a presentation given by Peter Barton Hutt, Esq., to the Dental Plaque Subcommittee on October 1998.

Mr. Hutt's opening remarks included a statement that "*prior panels and the FDA have always taken in these monographs, not for specific dosage forms but to permit all reasonable dosage forms*". Mr. Hutt recommended that there be no limitation on dosage forms, but that any dosage form that is "*suitable for topical administration to the teeth*" ought to be permitted under the monograph. Mr. Hutt commented that the prevailing philosophy in the FDA is to permit the widest possible variation of OTC drugs under the monograph as long as there is assurance of safety and effectiveness. Several examples were provided from other monographs of which a few quotations are provided below.

In the preamble to the OTC Anorectal Monograph⁷¹ published in the Federal Register, the following statement can be found, "*The panel did not intend to restrict ingenuity and product design as long as the product accomplishes the claimed effect and meet the same final formulation requirements of safety and effectiveness as any other dosage form. Other final monographs are similarly expansive in their permitted range of dosage forms.*"

In the topical antiinfective monograph, industry asked the FDA to specify in the monograph a particular dosage form, namely, antibacterial soap. And according to Mr.

⁷¹ Federal Resister: 53 (August 15, 1988) p. 30756

Hutt, once again FDA's thinking was, "*No, we don't need to do that. That is merely another dosage form of antiinfective, antibacterial, antimicrobial products, and there is no reason to specify the dosage form because our job in FDA, and the panel's job, and the monograph's job is to set forth the general criteria that will assure safety and effectiveness of these products in any dosage form, all dosage forms.*"

These, and other examples were then summarized into three key elements that govern the acceptability of OTC dose forms:

1. the dose form **MUST** be safe and able to effectively deliver the active to the site of action
2. there **MUST** not be any reason to limit or exclude a particular dose form (ex., potential for misuse)
3. **MUST** establish comparable effectiveness

The prevailing guidance should be established by considering dosage forms which are "*suitable for topical administration to the teeth*", that do not violate any of the principles outlined above. It was recommended that acceptable topical oral dose forms should include toothpaste, gels, lozenges, floss, spritz spray, mouthrinse, trays, a slow-release pellet affixed to the tooth and any other dose form that complies with the principles noted above. No one on the panel disagreed with Mr. Hutt's proposal to not limit dosage forms.

The discussions that followed Mr. Hutt's presentation focused on the scientific rationale for establishing permissible levels of an active ingredient in different dosage forms and the performance tests required to assure the effectiveness of the final formulation. This discussion also acknowledged that different dosage forms will most likely require different concentrations of the active ingredient to yield the same exposure (delivered dose) of the active.

It was recognized that the rationale for establishing permissible levels of an active ingredient in a different dosage form would need to be based on exposure, rather than concentration. For example, a dentifrice would always have a higher concentration of an active ingredient than a mouthrinse in order to deliver comparable levels of the active given a lower volume of dentifrice is used. It was proposed, and well received, that when establishing the upper limit of an active ingredient for different dosage forms, it is best to consider the milligram amount of the active to be delivered per dose rather than the concentration in the final product (ex., dentifrice would be ~10X more concentrated than a rinse to deliver the same exposure/dose).

Since safety has already been established for the actives, the upper allowable level of active in any oral dosage form should be based on the milligram amount contained in a delivered dose of the approved dose form. The lower permissible level, on the other hand, should be governed by effectiveness as demonstrated through performance or clinical testing. If no validated study design or reference standard has been established, effectiveness through performance testing should consist of a single 6-month clinical trial satisfying the standards established by this rulemaking.

The panel stratified dosage forms into two classifications, Traditional and Novel. Traditional dose forms were defined as dentifrice, gels, pastes, or rinses; while Novel dose forms include everything else not considered in the Traditional classification. Formulating a Category I approved active in any Traditional dose form requires the following:

- a. Active concentration within the mg/dose range recommended by the Subcommittee
- b. Successfully pass all required performance test
- c. Comply with all appropriate packaging and labeling regulations

For all Novel dose forms or for Traditional dose forms that cannot be evaluated using the recommended performance tests and methodologies, the panel recommended a single 6-month clinical trial to provide evidence of antiplaque and antigingivitis activity comparable to the approved dose form. In principle, if an alternative Traditional dose form (dentifrice, gel, paste, or rinse) can be evaluated via the same performance test and methodology as recommended for the Category I active, no clinical testing would be required. However, if the test methodology has to be modified in any substantial way, a single 6-month clinical trial is required. It is believed that the trial data will not need to be submitted to the Agency but must be available should the Agency request proof of efficacy.

There are numerous examples in the OTC Monographs where specific doses or concentrations of active ingredients are specified, but the monograph is either silent in regard to dose form or provides provisions for numerous dosage forms within the monograph. For example, the nasal decongestant monograph specifies an oral nasal decongestant as “a drug that is taken by mouth and acts systemically”, thus providing manufacturers the ability to formulate the product in a variety of dose forms – tablets, capsules, liquids, lozenge, etc. The same monograph allows for topical nasal decongestants in several dose forms – drops, jellies, sprays, or intranasally inhaled. Many monographs for topical drug products describe the dose form very broadly, “in a form suitable for topical application.” The monograph for topical acne drug products is such an example where only the concentration range for each active is specified, but there is no specific vehicle or dose form requirement. Similarly, in the monograph for topical antifungal products, the concentration range for each active is specified but no limitation is placed on dose form. In this case, the monograph actually tailors the directions for use to allow for language needed for aerosol products vs. those products that are rubbed on the skin. Likewise, the monograph for antidandruff products does not specify dose forms, and even takes into account differences in concentrations of active level needed for pyrrithione zinc products that are washed off after brief exposure and those that are left on the skin.

In order to maintain the flexibility needed to market other topical oral dose forms of antigingivitis/antiplaque active ingredients, the monograph should not limit dose forms for Category I active ingredients to only those dose forms that were reviewed by the Subcommittee and subsequently specified in the ANPR. We agree with the Subcommittee that one 6-month gingivitis study is sufficient to establish the safety and effectiveness of the alternate dose form. We believe such alternate dose forms could be marketed during the rulemaking process as long as the exposure of the active (amount of drug delivered to site of action) from the alternate dose form does not exceed the exposure defined by the monograph labeling and/or conventional usage patterns and effectiveness is established.

As a hypothetical example, a CPC dentifrice would represent an alternate dose form of the CPC mouthrinse which is recommended as a safe and effective Category I active in the Antigingivitis/Antiplaque ANPR. The dentifrice would be formulated approximately 10-times more concentrated to compensate for using approximately one-tenth the mouthrinse dose so that the resultant delivered dose of CPC from the dentifrice approximates the delivered CPC dose from the mouthrinse:

Subcommittee Recommended CPC Mouthrinse Concentrations

Concentrations:	0.045 – 0.1% CPC
Biological Availability:	72 – 77%
Dose:	20 ml
Dosing Frequency:	twice daily

Top of Range (maximum dosage)

20 mls of a 0.1% CPC rinse at 100% bioavailability, 2 x a day

$0.1/100 \times 20\text{ml} \times 2 \text{ uses/day} \times 1.0 = 40 \text{ mgs active CPC per day (20 mgs per dose)}$

Theoretical example for a dentifrice formulated to deliver an equivalent daily exposure as that recommended for a 0.1% CPC mouthrinse:

Concentrations (approx): 0.5 – 1.33% CPC
Biological Availability: $\geq 72\%$
Dose: 1.5 g
Dosing Frequency: twice daily

Top of Range (maximum dosage)

1.5 g of a 1.3% CPC dentifrice at 100% bioavailability, 2 x a day

$1.33/100 \times 1.5 \text{ g} \times 2 \text{ uses/day} \times 1.0 = \mathbf{39.9 \text{ mgs}}$ active CPC per day (20 mgs per dose)

We believe the Agency should provide flexibility in formulating alternate dose forms of Category I antigingivitis/antiplaque ingredients based on the principle that the delivered amount of active cannot exceed the maximum allotted exposure as determined by theoretical calculations (i.e., $\leq 20\text{mg}$ CPC per use). We believe that regulating formulations based on drug exposure (mg drug delivered/use) rather than a concentration is most appropriate for this rulemaking. This recommended approach would (1) ensure product safety as the exposure would not exceed that already proven safe, (2) provide industry with the ability to introduce a variety of safe and effective products to the marketplace to better meet consumer needs and (3) uniformly standardized formulations limits within specific dose forms. Importantly, it will minimize the regulatory burden to the Agency who would be required to review citizen petitions or NDAs for each alternate topical oral dose form.