

December 17, 2002

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Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20852

CITIZEN PETITION

Tom's of Maine ("Tom's") submits this citizen petition under 21 C.F.R. §§ 10.30 and 355.70 to ask the Food and Drug Administration ("FDA") to permit an alternative reference standard to be used in required biological testing of certain over-the-counter ("OTC") anticaries dentifrices.

A. Action Requested

FDA's OTC anticaries drug monograph (the "monograph") requires testing of fluoride dentifrices using an active control reference standard to confirm the bioavailability of the active fluoride ingredient in the finished fluoride formulation. 21 CFR § 355.70(a). The tests must be performed using the methods and procedures specified in the monograph, unless FDA permits otherwise in response to a citizen petition. Id. at (c). In particular, unless FDA authorizes an alternative, the active control dentifrice used in the required tests must be a United States Pharmacopeia reference standard fluoride dentifrice ("USP reference standard"). Id. at (b). The reference standards are "dentifrice formulations that have been demonstrated to be clinically effective and that were reviewed by the [OTC review] Panel." ¹

1. Anticaries Drug Products for Over-the-Counter Human Use, 60 Fed. Reg. 52,474, 52,502 (Oct. 6, 1995) (final monograph); see also Anticaries Drug Products for Over-the-Counter Human Use, 53 Fed. Reg. 22,430, 22,431-22,432 (June 15, 1988) (tentative final monograph); Anticaries Drug Products for Over-the-Counter Human Use Establishment of a

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CP10

Tom's of Maine manufactures and markets fluoride toothpastes which contain sodium monofluorophosphate ("MFP") in one of two different abrasive systems. Tom's Natural Fluoride Toothpastes for Children have a "dual" abrasive system composed of calcium carbonate (12.3% by weight) plus silica (5% by weight). Tom's Original Fluoride Toothpastes (Tom's Original) have a "single" abrasive system containing only calcium carbonate (49% by weight).²

Tom's plans to bring to market additional MFP toothpastes using calcium-only abrasive systems, and will have to test them pursuant to § 355.70(a). However, there is no USP reference standard available for calcium-only MFP dentrifices, and comparisons to the USP dual-abrasive MFP reference standard would be inappropriate. Fortunately, FDA has previously recognized that Tom's Original has the same composition as and was found comparable in biological testing to Maclean's Toothpaste, a calcium-only MFP dentrifice that was found by the panel and FDA to be clinically effective and bioavailable. Thus, Tom's Original is an appropriate reference standard for biological testing of new MFP calcium only dentrifices, and Tom's requests that FDA permit its use for that purpose.

B. Statement of Grounds

In addition to an active fluoride ingredient, anticaries dentrifices also contain one or more abrasive ingredients, some of which can affect the bioavailability of the fluoride.³ The

Monograph, 45 Fed. Reg. 20,666, 20,667 (March 28, 1980) (notice of proposed rule making) ("Panel Report").

2. The fluoride/abrasive compositions of Tom's and other dentrifices discussed in this petition are shown in Attachment 1.

3. Final monograph, 60 Fed. Reg. at 52,475; *id.* at 52,449–52,450.

testing required by 21 CFR § 355.70(a) assesses whether the abrasive system impairs the availability of the fluoride. The monograph contemplates that a USP standard reference dentifrice will be used as the active control in the required tests.⁴ Each of the available USP reference standards has the same fluoride/abrasive composition as a marketed product whose clinical effectiveness and bioavailability was established in the OTC review.⁵ A dentifrice that performs at least as well in the required tests as its USP reference standard is considered sufficiently bioavailable to be marketed without additional clinical testing. A product that does not satisfy one or more of the required tests by reference to the USP standard control dentifrice cannot be presumed clinically effective without product-specific testing (and an approved NDA).

As Tom's has already documented in a previous citizen petition,⁶ the anticaries advisory panel reviewed extensive clinical and other data on Macleans Toothpaste, an MFP calcium-

4. 21 C.F.R. § 355.70(b).

5. See Supra note 1.

6. The previous citizen petition sought FDA's permission to use an alternative test method for Tom's MFP dentifrices, instead of one of those specified in 21 C.F.R. § 355.70. That petition is filed in the OTC anticaries review docket (No. 80N-0042, or "the docket") as 80N-0042/CP5 (Feb. 16, 1996) ("the 1996 petition"), together with subsequent supplements filed as 80N-0042/ SUP3 (March 15, 1996), SUP4 (May 6, 1996), SUP5 (June 12, 1996), SUP7 (August 7, 1996), and SUP8 (Sept. 11, 1996). FDA's response to the 1996 citizen petition is filed as 80N-0042/ LET38 (Letter from Debra A. Bowen, M.D. to Jane E. Baluss, Sept. 27, 1996) ("1996 Petition Response"). All of the cited submissions are incorporated by reference herein.

Some of the evidence that Tom's submitted to support its 1996 citizen petition was already on record in Docket 80N-0042, and this petition also relies part on evidence previously submitted to the docket by Tom's and others. As a general rule, this petition will cite such information by the docket designation for its previous submission by Tom's e.g.: "80N-0042/CP5, Exhibit A."

only dentifrice.⁷ The panel relied on those data as evidence that MFP is a safe and clinically effective fluoride source.⁸ Furthermore, the monograph testing profiles for MFP/calcium carbonate dentifrices were directly based on data from bioavailability testing of Macleans, and it was expected that the USP reference standard for MFP/calcium carbonate dentifrice testing would be manufactured and supplied by Beecham using the Macleans formula.⁹ As it happened, however, by the time the anticaries monograph and USP reference standards were finalized, Beecham had stopped marketing Macleans in the United States, and the USP reference standard was based instead on its marketplace successor, AquaFresh Toothpaste. Like Macleans, Aquafresh contained MFP, but unlike Macleans, it had a dual abrasive system composed of equal parts calcium carbonate and silica.¹⁰ Thus, the USP reference standard based on Macleans toothpaste contains both calcium carbonate and silica in its abrasive system rather than the calcium-only abrasive system actually found in the toothpaste the panel and FDA concluded was effective and bioavailable. (The product is described on the USP's website as an MFP "calcium carbonate" dentifrice,¹¹ but its abrasive system contains both 12%

7. The OTC advisory panel specifically identified Macleans as one of the products reviewed as a basis for its conclusions on safety and efficacy. Tom's 1996 petition and related supplements contained extensive data on Macleans that reviewed by the Advisory Panel. FDA's response to Tom's 1996 petition reaffirmed the clinical efficacy of Macleans based on a de novo renew of data resubmitted by Tom's. 80N-0042/LET 38 at 2.

8. 80N-0042/SUP4 at 4 and Exhibits 4-7.

9. 80N-0042/SUP4 at 4 and Exhibit 4.

10. Attachment 1; 80N-0042/CP5, Exhibit G.

11. [Http://www.usp.org](http://www.usp.org); see also 60 Fed. Reg. at 52,501 (describing dual abrasive USP standard as "[MFP]- calcium carbonate").

calcium carbonate and 12% silica.¹²⁾ The USP does not offer a calcium-only MFP reference standard.

Because calcium carbonate has a comparatively greater potential to react with MFP than does silica,¹³ an abrasive system that contains significant amounts of silica is not an appropriate comparator for calcium only products. In fact, FDA has previously concluded that dual-abrasive and calcium-abrasive dentifrice formulations are significantly different from each other and therefore require correspondingly different reference standards. This issue was squarely raised in Tom's previous citizen petition, in which Tom's sought to use an alternative test method to satisfy one of the monograph-required tests for all of its MFP toothpastes.¹⁴ The active control dentifrice used in the study under consideration on that petition was Macleans toothpaste. In addition to the results of its alternative test, Tom's presented detailed information to show that Maclean's Toothpaste and Tom's Original were analytically similar.¹⁵ After reviewing the OTC review record on Maclean's, FDA explicitly concluded that Macleans dentifrice "was an acceptable reference standard" for products made with Tom's "original" MFP calcium-only formulation, including Tom's Original.¹⁶ FDA

12. Attachment 1.

13. 80N-0042/SUP4, Exhibit 14 at 438.

14. Specifically, Tom's 1996 citizen petition asked FDA to accept data from an in situ remineralization/demineralization test in humans, instead of the monograph-specified animal caries test.

15. 80N-0042/SUP7.

16. 80N-0042/LET 38 at 2. Letter from Debra R. Bowen to Jane E. Baluss, Sept. 27, 1996, 2 (Exhibit 4, attached). See also 80N-0042/PDN (Letter from Dennis E. Baker, Associate Commissioner for Regulatory Affairs to Daniel R. Dwyer, Esq.), Aug. 26, 1999 (reiterating

further concluded that the dual abrasive USP reference standard is “significantly different from the abrasive systems in Tom’s original toothpaste formulation” for purposes of selecting an appropriate reference standard in monograph-required dentifrice testing.¹⁷ Accordingly, the agency required Tom’s to conduct separate bioavailability testing of its dual abrasive MFP toothpastes, using the USP dual abrasive reference standard.¹⁸

Although those conclusions arose from FDA’s consideration of appropriate reference standards for use with a specific alternative test method, they also compel the conclusion that the proper comparator for an MFP calcium-only toothpaste is an MFP calcium-only reference standard. As discussed above, Maclean’s Toothpaste would be effective and bioavailable. But as far as Tom’s is aware, Maclean’s Toothpaste in the MFP single abrasive formula considered in the OTC review is no longer available anywhere in the world. But Tom’s Original, which is similarly formulated and was found to be comparable to Maclean’s Toothpaste in biological testing acceptable to FDA, is available, and is appropriate for use as a reference standard in biological testing for MFP toothpastes containing the single abrasive calcium carbonate. Allowing Tom’s Original to be used as a reference standard for calcium-only MFP dentifrices would repair an unintentional gap in the list of reference standards, and make possible a wider variety of effective MFP dentifrices than would otherwise be the case.

FDA need not and should not require formal revision of the current USP standard to include a single abrasive reference standard as a precondition to granting this petition. FDA

FDA conclusion that Tom’s calcium-only and dual abrasive MFP dentifrices “contain different-abrasives” for purposes of monograph-required testing).

17. 80N-0042/LET 38 at 2.

18. Id.

statements in the OTC record clearly contemplate that any formulation that was specifically reviewed and found to be effective by the advisory panel would be an appropriate reference standard for a dentifrice with the same fluoride/abrasive composition.¹⁹ Consistent with that logic, FDA's response to Tom's earlier petition explicitly accepted Macleans toothpaste as an appropriate reference standard for Tom's Original MFP dentifrices, notwithstanding its non-USP status. Furthermore, even though FDA did require Tom's to use the dual abrasive USP reference standard when testing Tom's dual-abrasive dentifrices there is no reason to extend that requirement to silica-free formulations for which an official reference standard is manifestly not available.

Conclusion

For the reasons discussed above, Tom's believes that FDA can and should allow it to perform required testing of its MFP dentifrices using Tom's Original calcium only toothpaste as the reference standard dentifrice.

C. Environmental Impact

The action requested qualifies for categorical exclusion from the requirement of issuance of an environmental assessment under 21 C.F.R. § 25.31(a). Tom's does not believe that any environmental impact will result from the granting of this petition.

D. Economic Impact

In accordance with 21 C.F.R. § 10.30(b), Tom's will provide data concerning the economic impact of the action sought if requested by the Commissioner.

19. Tentative Final Monograph, 53 Fed. Reg. at 22,434; Final Monograph, 60 Fed. Reg. at 52,499-52,500.

E. Certification

Tom's certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to Tom's that are unfavorable to the petition.

Respectfully submitted,

Of Counsel:

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ATTACHMENT 1

FLUORIDE/ ABRASIVE COMPOSITION OF MFP/ CALCIUM CARBONATE
DENTIFRICE FORMULATIONS *

<u>ACTIVE INGREDIENT:</u>	<u>USP REF. STD. & AQUAFRESH</u>	<u>MACLEANS</u>	<u>TOM'S ORIGINAL</u>	<u>TOM'S CHILDREN'S</u>
MFP	0.76	0.76	0.76	0.76
<u>ABRASIVE(S)</u>				
CALCIUM CARBONATE	7.1	38.0	49.0	5.49
SILICA	12.0	—	—	5.0

* 80N-0042/CP5, Exhibit A.

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ATTACHMENT 2



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

0205 '96 OCT 29 A11:14

Food and Drug Administration
Rockville MD 20857

SEP 27 1996

Jane E. Baluss, Esquire
Buc & Beardsley
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Washington, D.C. 20036-5800

Re: Docket No. 80N-0042
Comments No. CP5, PSA5, and
SUP3 through SUP8

Dear Ms. Baluss:

This letter is in response to your citizen petitions on behalf of Tom's of Maine (Tom's), dated February 20, 1996 and September 11, 1996. The petitions were filed as CP5 and PSA5, respectively, under Docket No. 80N-0042 in FDA's Dockets Management Branch. You submitted supplementary information on March 15, 1996 (SUP3), May 6, 1996 (SUP4), June 12, 1996 (SUP5), August 7, 1996 (SUP6), August 26, 1996 (SUP7), and September 11, 1996 (SUP8).

In one petition (CP5), you requested that the agency accept the results of an intra-oral remineralization test in human subjects to demonstrate the bioavailability of the fluoride ion in Tom's Natural fluoride toothpastes, in lieu of the animal caries reduction test that otherwise would be required under § 355.70 of the final monograph for over-the-counter (OTC) anticaries drug products. In addition, you contended that the intra-oral test results of Tom's "original" sodium monofluorophosphate (MFP)/calcium carbonate formulation could support the position that animal testing also should not be required for Tom's other fluoride toothpastes, which are closely similar in formulation both to each other and to clinically-tested commercial dentifrices.

In a second petition (PSA5), you requested that the agency stay the animal caries testing requirement under § 355.70(a) of the final monograph for OTC anticaries drug products with respect to Tom's Natural Toothpaste drug products, while Tom's testing petition (CP5) remains under consideration by the agency, and for such further time as may reasonably be needed for Tom's to complete additional testing or take any other action required by the agency's decision on that petition.

The Division of OTC Drug Products has reviewed the data and information contained in the petitions and supplements and has determined that the intra-oral remineralization study as conducted appears acceptable to demonstrate sufficient fluoride bioavailability of Tom's original dentifrice formulation. However, we do not consider the study adequate to support the

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effectiveness of Tom's other sodium MFP-containing dentifrice formulations with different abrasive concentrations and combinations. We have the following comments:

As discussed at our meeting on March 20, 1996, we had a number of concerns about the study methodology. Although we have considered the results as acceptable for this one study, we believe that the treatment of the enamel specimens in an intra-oral appliance assay should simulate as closely as possible the normal exposure of teeth to both the dentifrice and to various cariogenic factors. The Division is particularly concerned with the disposition of the appliance during meals and the precise technique by which the dentifrice is applied. We recommend that protocols for any future intra-oral appliance assay be submitted to us for review prior to initiation of the assays.

As you are aware, the OTC anticaries final monograph requires that a United States Pharmacopeia (USP) fluoride dentifrice reference standard must be used in any biological tests conducted to determine fluoride bioavailability. We are aware that at the time the intra-oral appliance study was done the USP dentifrice reference standard program was not established and, therefore, the Macleans toothpaste was used as the dentifrice reference standard in this study. We have reviewed the two clinical studies submitted in the petition in support of the effectiveness of Macleans toothpaste as an appropriate reference standard in the intra-oral appliance study. Based on one of the studies demonstrating the effectiveness of the Macleans dentifrice formulation, we have concluded that it was an acceptable reference standard in the intra-oral appliance study. However, because reference standards are now available, only an official USP dentifrice reference standard will be acceptable in future fluoride bioavailability studies. In addition, as you know, § 355.70(a) of the anticaries final monograph requires that Tom's original formulation must also meet one of the following tests: Enamel solubility reduction or fluoride enamel uptake. Although it is not required, we have not been presented with any data from either of these tests.

We do not consider the results of the intra-oral study for Tom's original formulation containing 49 percent calcium carbonate applicable to Tom's two other sodium MFP-containing toothpaste formulations containing 35 percent calcium carbonate/15 percent baking soda and 12.3 percent calcium carbonate/5 percent silica, respectively. We consider the abrasive systems in Tom's other two sodium MFP-containing dentifrice formulations significantly different from the abrasive system in Tom's original toothpaste formulation. Thus, we consider it necessary that each of Tom's other dentifrice formulations included in the petition be specifically tested to show that it meets the biological testing requirements as well as the enamel solubility reduction or fluoride enamel uptake test to support anticaries effectiveness.

In response to Tom's request for additional time to complete the biological testing requirements under § 355.70, we point out that a similar request was submitted by the Joint Oral Care Task Group of the Nonprescription Drug Manufacturers Association (NDMA) and the Cosmetic,

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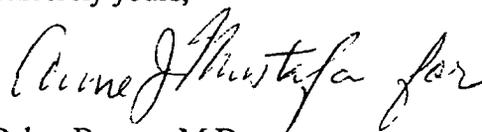
Toiletry, and Fragrance Association (CTFA) (the Task Group) . In my recent letter of September 23, 1996 to the Task Group, I indicated our intention to recommend that the Associate Commissioner for Regulatory Affairs provide industry a 1-year extension of the effective date for the biological testing requirement portion of the anticaries final monograph from October 7, 1996, to October 7, 1997. A notice will appear in a future issue of the Federal Register indicating that additional time is being provided for industry to comply with the biological testing requirements (§ 355.70(a)) for OTC anticaries drug products.

The 1-year extension granted to industry to complete the biological testing requirements will provide Tom's sufficient time to conduct the biological studies for its other products. If Tom's intends to conduct an intra-oral study in lieu of the animal caries reduction test for its two other sodium MFP-containing dentifrice formulations, we recommend that Tom's submit to the agency the study protocol at its earliest convenience before beginning such studies. This information should be sent to FDA's Dockets Management Branch along with a desk copy to the Division of OTC Drug Products.

We intend to recommend that the Associate Commissioner for Regulatory Affairs respond to your petitions in the above manner. Any comments you may wish to make on the above information should be submitted in three copies, identified with the docket and the comment numbers that appear at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, Room 1-23, Rockville, Maryland 20857. This letter should not be considered a formal ruling on your petition. That occurs when you are sent a response by the Associate Commissioner for Regulatory Affairs.

We hope this information will be helpful.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Debra Bowen for".

Debra Bowen, M.D.

Director

Division of OTC Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research