

# Efficacy Trends of an Aging U.S. Pharmacopeia Reference Dentifrice

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## ABSTRACT

**Introduction:** United States Pharmacopeia dentifrice reference standards are required for mandatory FDA Anticaries Monograph testing (ESR or EFU, and Rat Caries, or in the case of Tom's of Maine, an *In situ* Caries Model). The choice of reference standard depends on the abrasive system/fluoride source of the prototype toothpaste.

**Objective:** To compare the efficacy of a prototype all-natural silica/NaMFP dentifrice, a commercially purchased silica/NaMFP dentifrice and the current (and only available) USP Sodium Monofluorophosphate (1000ppm)/Silica Reference Dentifrice (Lot PTG 07-40).

**Methods:** Product efficacy was evaluated using an enamel fluoride uptake method identical to the one identified as Procedure 40 in the FDA Monograph, with the following exception: lesions were formed using a solution of 0.1M lactic acid/0.2% Carbopol 907 50% saturated with HAP at a pH of 5.0. Fluoride analyses were performed with a fluoride ion specific electrode and pH analyzer. Samples and standards were prepared by aqueous dilution mixed with an equal volume of TISAB II.

**Results:** Increases in incipient lesion enamel fluoride content were as follows: USP Reference (837±28ppm), commercial toothpaste (662±24ppm), and natural prototype (619±26ppm). Measured ionic fluoride levels of the pastes were: USP (60±1ppm), commercial toothpaste (28±1ppm), and natural prototype (25±1ppm).

**Conclusions:** The USP reference dentifrice was significantly more effective than the other two dentifrices tested with regard to promoting incipient lesion enamel fluoride uptake. The Tom's of Maine prototype and AIM® Cavity Protection (Unilever) did not differ significantly. The USP silica/MFP reference (lot PTG 07-40) was manufactured on August 26th, 1997, and originally contained 24ppm free ionic fluoride. Although stored frozen, USP lot PTG 07-40 has continued to hydrolyze PO<sub>3</sub>F<sup>2-</sup> into F<sup>-</sup>, thus rendering it *more* efficacious in FDA-required bioavailability testing. The United States Pharmacopeia should order fresh reference standard upon request.

## INTRODUCTION

United States Pharmacopeia dentifrice reference standards are required<sup>1</sup> as positive controls in FDA-mandated bioavailability<sup>2</sup> Anticaries Monograph tests. The choice of reference dentifrice standard depends on the abrasive system/fluoride source of the prototype toothpaste under investigation. Because drug products typically lose efficacy as actives react/degrade over time, USP uses low temperature storage (freezing) to impede active degradation and to preserve efficacy. Sodium monofluorophosphate (NaMFP) is an exception to this rule. Although inhibited by low temperature storage, monofluorophosphate (PO<sub>3</sub>F<sup>2-</sup>) does hydrolyze into ionic fluoride, F<sup>-</sup>. The bioavailable level of ionic fluoride (F<sup>-</sup>), whether from sodium fluoride or sodium monofluorophosphate, is the critical component of a dentifrice's efficacy. It has been reported<sup>3</sup> that sodium fluoride (i.e., F<sup>-</sup>) is significantly more effective than NaMFP (i.e., PO<sub>3</sub>F<sup>2-</sup>) in preventing caries. Thus, one can conclude that ionic fluoride will outperform PO<sub>3</sub>F<sup>2-</sup> in mandated bioavailability testing.

## OBJECTIVES

The primary objective of this research was to demonstrate that an aged USP Sodium Monofluorophosphate (1000ppm)/Silica Reference Dentifrice (Lot PTG 07-40) had increased in efficacy to the point that it should be replaced by fresh sample. A secondary objective is to convince the USP that some form of efficacy testing, not FDA fresh release limits of fluoride, should be the criteria used to assign expiry dating on their NaMFP/silica reference dentifrice.

Table I. Ionic fluoride values as of October 2003.

Dentifrice	Ionic fluoride(ppm)
USP Reference PTG 07-40	60±1
AIM Cavity Protection	28±1
Tom's Prototype	25±1

Table II. Ionic fluoride values of the Tom's of Maine prototype dentifrice manufactured August 16, 2002.

Description	F <sup>-</sup> (ppm)	PO <sub>3</sub> F <sup>2-</sup> (ppm)	Total Fluoride (ppm)
Initial	16	1,082	1,098
1M@25°C	16	--	--
2M@25°C	20	--	--
5M@25°C	21	--	--
11M@25°C	24	1,041	1,065
29M@25°C	28	1092	1,120
6M@25°C, then 5M@40°C	47	992	1,039
6M@40°C	63	--	--

## MATERIALS & METHODS

**Materials:** AIM Cavity Protection (lot 07233J00) was purchased at a local Kennebunk market, while the Tom's of Maine prototype was a GMP factory-manufactured pilot batch. The silica/MFP reference dentifrice was purchased from USP.

**Methods:** Enamel fluoride uptake employing FDA Procedure 40 was performed at Indiana University School of Dentistry Oral Health Research Institute. Ionic fluoride analyses were performed with a fluoride ion specific electrode (Thermo Orion Model 96-09) and pH analyzer (Mettler-Toledo Model MA235). Samples and standards were prepared by aqueous dilution mixed with an equal volume of TISAB II. Fluorophosphate analyses were performed on a Hewlett Packard HPLC System equipped with an Asahipak ODP-50 column and a Diode Array Detector.

## RESULTS & DISCUSSION

Under normal manufacturing conditions fresh values of ionic fluoride in silica/NaMFP dentifrices are typically in the range of 15-30ppm. Table I displays ionic fluoride content of the three toothpastes as measured days prior to EFU evaluation. As it was 6 years/2 months old at the time of testing, the USP Silica/NaMFP Reference Dentifrice contained roughly 2.3 times more ionic fluoride than the other dentifrices. Figure 1 shows the results of the EFU study performed in October 2003. The USP reference was significantly more effective than the other two dentifrices tested with regard to promoting incipient lesion enamel fluoride uptake. The Tom's of Maine prototype anticavity gel toothpaste and AIM Cavity Protection were similar but less effective than the USP reference. However, as Figure 2 displays, a Certificate of Analysis of the USP dentifrice clearly shows it contained 24ppm ionic fluoride (in line with the two fresh samples of this investigation) as of January 29, 2001 (it was manufactured on August 26, 1997). Table II displays the results of the stability investigation of the Tom's of Maine prototype dentifrice. After almost three years the prototype appears to be starting to hydrolyze ionic PO<sub>3</sub>F<sup>2-</sup> into ionic fluoride. However, at 28 ppm the ionic fluoride is still only half the level present in the USP. Prototype dentifrice samples placed in accelerated stability conditions take five to six months for the ionic fluoride levels to reach those of the USP reference, which by definition of the Arrhenius equation<sup>4</sup> ( $\log(k'/k) = E_a/2.3R(1/T_2 - 1/T_1)$ ) would correlate to between five and six years under ambient conditions.

## CONCLUSIONS

Although USP reference dentifrices are stored frozen, hydrolysis of PO<sub>3</sub>F<sup>2-</sup> to F<sup>-</sup> is not totally inhibited. The USP should develop efficacy screens to establish expiry dating of reference samples, or provide fresh reference dentifrice upon request. Using USP reference material in *in situ* caries models exceeds \$25,000/study. Companies should not have to gamble on passing \$200,000-\$300,000 clinical studies because of chemically compromised reference standards.

## REFERENCES

- <sup>1</sup>21 CFR § 355.70[b].
- <sup>2</sup>Federal Register Volume 60 No. 194 p. 522497, October 6, 1995.
- <sup>3</sup>Caries Research, Vol. 27, No. 4., pp. 337-360, 1993.
- <sup>4</sup>*Chemistry-The Central Science*, 2ND Edition, Theodore L. Brown and H. Eugene LeMay, Jr., Prentice Hall, Inc. Englewood Cliffs, New Jersey, 07632, pp. 395-396, 1981.

