APhA
American Pharmacists Association

July 16, 2025

[Submitted electronically to www.regulations.gov]

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: [Docket No. FDA-2025-N-1557] Use of Orally Ingestible Unapproved Prescription Drug Products Containing Fluoride in the Pediatric Population; Public Meeting; Establishment of a Public Docket; Request for Comments

Dear Commissioner Makary:

The American Pharmacists Association ("APhA") appreciates the opportunity to submit comments to the Food and Drug Administration ("FDA"), and the Department of Health and Human Services ("HHS") on the request for comments titled "Use of Orally Ingestible Prescription Drug Products Containing Fluoride in the Pediatric Population," including the current clinical uses of orally ingestible products, safety concerns regarding these products, continued use, and impacts of removing these products from the market.

APhA is the largest association of pharmacists in the United States, advancing the entire pharmacy profession. APhA represents pharmacists, scientists, student pharmacists, and pharmacy technicians in all practice settings, including but not limited to community pharmacies, hospitals, long-term care facilities, specialty pharmacies, community health centers, physician offices, ambulatory clinics, managed care organizations, hospice settings, and government facilities. Our members strive to improve medication use, advance patient care, and enhance public health.

According to data from the Medical Expenditure Panel Survey (MEPS) 2013-2022, more than 1.7 million prescriptions for sodium fluoride were dispensed in 2022 alone.[1] As an indigestible product only available by prescription, pharmacists must be involved in the use of fluoride in the care of pediatric patients. As essential health care providers, pharmacists play a critical role in ensuring that patients have access to their medications and take them as prescribed. When

[1] *Sodium Fluoride Drug Usage Statistics, United States, 2013-2022*, ClinCalc.com (Apr. 15, 2025). Available at: https://clincalc.com/drugstats/Drugs/SodiumFluoride#:~:text=Drug%20Cost%20Over%20Time%20(2013%20%2D%202022),fill%20divided%20by%20the%20days%20of%20therapy.

filling each prescription and providing direct patient care, pharmacists strive to ensure that they make informed, evidence-based decisions that support optimal patient outcomes.

APhA offers the following responses to the specific questions for discussion at the public meeting:

1. Please comment on the evidence supporting the current clinical uses of orally ingestible unapproved prescription drug products containing fluoride for tooth decay prevention in the pediatric population.

Clinical Rationale:

- Evidence from randomized clinical trials and systematic reviews shows fluoride supplements are effective in reducing dental caries.[2]
- In a July 2025 submission to FDA, the American Dental Association (ADA) emphasized that the majority of peer-reviewed scientific evidence supports the safety and efficacy of fluoride supplements at recommended levels. ADA cited studies showing that fluoride ingestion at therapeutic doses does not significantly impact neurological development, thyroid function, or gut health. Additionally, ADA has stated that fluoride supplements are a valuable tool in preventing dental caries, particularly for children who lack access to fluoridated water.[3]
- The U.S. Preventive Services Task Force (USPSTF) has previously found fair evidence that oral fluoride supplements reduce dental caries in preschool children with low fluoride exposure.[4]

APhA appreciates the concern for evidence-based clinical decision making. Dietary fluoride supplements, although not formally FDA-approved as prescription drugs for this use, are clinically recommended by authoritative bodies such as the ADA and the USPSTF.[5] These

[2] *Guideline on Fluoride Therapy*, American Academy of Pediatric Dentistry (2014). Available at: https://www.aapd.org/globalassets/assets/1/7/g_fluoridetherapy1.pdf
[3] Olivia Andersdon, ADA Defends Safety and Efficacy of Fluoride Supplements Amid FDA Review, ADANews (July 11, 2025). Available at: https://adanews.ada.org/ada-news/2025/july/ada-defends-safety-and-efficacy-of-fluoride-supplements-amid-fda-review/.
[4] *Prevention of Dental Caries in Children Younger Than Five Years: Screening and Interventions*, U.S. Preventive Services, U.S. Preventive Services Task Force (Dec. 7, 2021). Available at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/prevention-of-dental-caries-in-children-younger-than-age-5-years-screening-and-interventions1.
[5] *Id.*

supplements are intended for children over 6 months of age who are at high risk of tooth decay and do not have access to fluoridated drinking water, which is common in rural communities. Oral fluoride supplementation is determined on a patient-by-patient basis, dependent on that child's age, weight, and exposure to fluoride in other areas of life.

2. Please comment on the safety concerns associated with these drug products, taking into account the amount of fluoride they provide when used as directed for prevention of tooth decay prevention in the pediatric population.

Safety:

- The National Toxicology Program (NTP) monograph identified an association with high levels of fluoride and lower IQ.[6] The NTP website clarifies that this association "does not prove a cause and effect."[7] Additionally, the NTP meta-analysis was based on 19 studies conducted in six countries, in areas where the fluoride content in drinking water is significantly higher than what is typically found in the United States, and more than double the amount recommended by the U.S. Public Health Service for community water fluoridation.
- Many concerns regarding fluoride's effect on the gut microbiota stem from peer-reviewed animal studies, which have yielded mixed results at best. An FDA press release noted that "none of the studies retrieved examined the effects of ingested fluoridated water on the human microbiome."[8]
- The NTP[9] and other systematic reviews[10] have found that high fluoride exposure may affect thyroid hormones; however, there's no conclusive evidence that fluoride at recommended levels harms thyroid function.

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[6] NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopment and Cognition: A Systematic Review, National Toxicology Program (Aug. 2024). Available at: https://ntp.niehs.nih.gov/sites/default/files/2024-08/fluoride_final_508.pdf.

[7] *Fluoride Exposure: Neurodevelopment and Cognition*, National Toxicology Program. Available at: https://ntp.niehs.nih.gov/research/assessments/noncancer/completed/fluoride.

[8] Gary P. Moran, et al., *Does Fluoride Exposure Impact on the Human Microbiome?*, 379 Toxicology Letters 11 (2023). Available at: https://www.sciencedirect.com/science/article/pii/S037842742300098X?via%3Dihub.

[9] Inga Iamandii, et al., *Does Fluoride Exposure Affect Thyroid Function? A Systematic Review and Dose-Response Meta-Analysis*, 252 Environmental Research 117759 (2024). Available at: https://www.sciencedirect.com/science/article/pii/S001393512302563X?via%3Dihub.

[10] *Information Paper – Water Fluoridation: Dental and Other Human Health Outcomes*, Australian Government National Health and Medical Research Council (July 2017). Available at: https://www.nhmrc.gov.au/about-us/publications/water-fluoridation-dental-and-other-human-health-

APhA appreciates the concern for the safety of these drug products while acknowledging that risks for this population may exist without proper supplementation. In non-fluoridated communities, fluoride supplements are the primary option for individuals to obtain the recommended amount of fluoride and prevent tooth decay. APhA also acknowledges that oral hygiene and oral health are fundamental to the overall health and well-being of patients.

3. Based on the totality of the data available today, please comment on the continued use of these drug products for tooth decay prevention in the pediatric population considering the additional sources of fluoride available.

Fluoridation:

- ADA recommends fluoride supplements for children at high risk of tooth decay who live in areas where the primary source of water is deficient in fluoride.[11]
- ADA daily fluoride supplement schedule for children is based on fluoride ion level in drinking water and the age of the child; this schedule does not recommend any supplementation for children when the drinking water fluoride level is >0.6mg/L.[12]

Although other routes of fluoride supplementation are often used (e.g., toothpaste, mouthwash, gel), consistent exposure to fluoridated products, whether oral hygiene products or tap water, is a component of healthy supplementation in daily living. Removing fluoride supplementation from other sources may result in an overall lack of ideal fluoride levels, which can hinder the prevention of cavities and tooth decay in pediatric patients.

4. From the perspective of patients and clinicians, what are the potential impacts of removing these drug products from the market? Are there alternatives to use of these ingestible drug products to achieve these ends?

Access:

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outcomes#block-views-block-fileattachments-content-block-1. *See also* NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopment and Cognition: A Systematic Review, National Toxicology Program (Aug. 2024). Available at: https://ntp.niehs.nih.gov/sites/default/files/2024-08/fluoride_final_508.pdf.

[11] R. Gary Rozier, et al., *Evidence-Based Clinical Recommendations on the Prescription of Dietary Fluoride Supplements for Caries Prevention*, 141 Journal of the American Dental Association 1480 (2010). Available at: https://jada.ada.org/article/S0002-8177(14)60477-3/pdf.

[12] *Id.*

- While community water fluoridation is ideal for pediatric populations, prescription-strength fluoride supplements may be a vital option for populations that are unable to access fluoride in other ways.

APhA is concerned that removing ingestible oral formulations of prescription fluoride products could hinder health care providers' clinical decision-making in the best interests of the patient. APhA is also concerned that removing these products, which continue to benefit pediatric patients, would lead to gaps and detriments in a child's health journey. While alternative options may exist for patients to obtain fluoride, pharmacists recognize that health care providers will prescribe different treatments for individual patients, and no single therapy is universally appropriate. As such, each patient's needs and circumstances must guide a health care provider's individualized care decision, which can include the prescribing and use of ingestible oral formulations of prescription fluoride. APhA values the expertise of dental professionals and trusts them to follow clinical guidelines and utilize their training and professional judgment on fluoride supplementation through ingestible oral formulations, as dentists and patients trust their pharmacists' expertise on medications.

Within the United States, a few states have taken steps to eliminate or reduce access to fluoridated water at the state and municipal levels. As such, ensuring the availability of orally ingestible prescription fluoride is essential to safeguard the oral health of vulnerable pediatric patients. Accordingly, APhA urges FDA and HHS to consider the broader public health implications of removing oral prescription fluoride products from the market. Orally ingestible fluoride plays a crucial role in preventing dental caries, particularly among pediatric patients, and its absence would have long-term consequences not only for a patient's oral health but also for their overall health. If you have any questions, require additional information, or would like to meet with APhA, please contact Corey Whetzel, APhA's Senior Manager, Regulatory Affairs, at cwhetzel@aphanet.org.

Sincerely,

Michael Baxter

Michael Baxter
Vice President, Government Affairs