



FLUORIDEALERT.ORG

Fluoride Action Network

April 12, 2016

Stefano Pessina
CEO, Walgreens
104 Wilmot Rd
Deerfield, IL 60015

Dear Mr. Pessina:

The purpose of this letter is to notify you that Walgreens is currently violating both federal and state law by selling prescription drugs (i.e., sodium fluoride drops and tablets) that have never been approved as either safe or effective by the Food & Drug Administration (FDA). The fact that these drugs have never been approved, and thereby illegal to sell per 21 U.S.C. § 331(d), has been confirmed in a recent FDA Warning Letter to a manufacturer of these drugs.

Not only is Walgreens currently selling these unapproved drugs, but, as detailed below, a recent investigation found that Walgreens is providing customers with false and misleading information about the FDA approval status and indications of these drugs, in possible violation of 21 U.S.C. § 331(k).

The imperative for removing these non-FDA approved drugs takes on added urgency in light of recent medical research linking fluoride ingestion during infancy and early childhood to serious health effects, including learning and behavioral disorders, thyroid disruption, impaired insulin production, and possibly cancer. Further, although the sole purpose of these drugs is to prevent tooth decay, current research shows they actually do more harm than good to teeth, by causing a disfiguring condition of the enamel known as dental fluorosis, while providing a "marginal at best" reduction in cavities.

After you read the information and documentation enclosed herein, I trust you will correct these ongoing violations by ordering that these unapproved fluoride drugs be removed from your pharmacies until such time as they are approved by the one and only government agency with the authority to do so: the FDA.

1. FDA WARNING ON FLUORIDE DROPS/TABLETS

On January 13, 2016, the FDA issued a Warning Letter to Kirkman Laboratories, Inc., in which FDA called on Kirkman to immediately discontinue marketing sodium fluoride drops and tablets. FDA issued the letter because sodium fluoride drops and tablets are "unapproved new drugs," and thereby illegal to introduce into interstate commerce. (A copy of FDA's Letter is enclosed as Appendix A.)

By way of background, fluoride drops and tablets are drugs because, per 21 U.S.C. § 321(g)(1), "they are intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans" (i.e., prevention of tooth decay). Further, as the FDA

prevention of disease in humans" (i.e., prevention of tooth decay). Further, as the FDA explains in its Warning Letter, fluoride drops and tablets are "new drugs"¹ within the meaning of 21 U.S.C. § 321(p) "because they are not generally recognized as safe and effective" for the purpose of preventing dental decay.²

FDA's conclusion that fluoride drops/tablets are "not generally recognized as safe and effective" is abundantly supported by recent research (discussed below), which shows that fluoride *ingestion* during early childhood causes dental fluorosis and potentially other serious harm, including impaired brain development, endocrine disorders, and cancer, while providing little, if *any*, role in cavity prevention. As noted by a review in the *Journal of Public Health Dentistry*: "Fluoride supplements, when ingested for a preeruptive effect by infants and young children in the United States, carry *more risk than benefit*."³ Other reviews have reached similar conclusions.⁴

Since FDA considers sodium fluoride drops and tablets to be "new drugs," they can only be legally introduced into interstate commerce if FDA has approved a "new drug application" under the rigorous standards set forth in 21 U.S.C. § 355 and 21 C.F.R. § 314.126. The FDA's Warning Letter confirms, however, that FDA has *never* approved *any* new drug application for fluoride drops/tablets. Accordingly, it is illegal under 21 U.S.C. § 331(d) for Walgreens to introduce these drugs into interstate commerce.

The fact that fluoride drops and tablets have never been approved by FDA should not actually come as a surprise to Walgreens. As detailed below, the FDA and National Library of Medicine have online databases which readily confirm that FDA has not approved the specific fluoride drops and tablets that Walgreens is currently selling, or any other fluoride drops and tablets. In any event, now that this issue is squarely before you, I assume you will take the necessary actions to ensure that Walgreens is acting in accord with the law.

¹ "The mere fact that a drug product has been marketed for an extended period does not preclude a finding of 'new drug' status." *United States v. Articles of Drug Hormonin*, 498 F. Supp. 424, 432 (D.N.J. 1980).

² Implicit in FDA's conclusion that sodium fluoride drops/tablets are "new drugs" is the correct recognition that these drugs do not qualify under 21 U.S.C. § 321(p)'s "grandfather" clause. To qualify under the grandfather clause, the drug must have been on the market prior to June 25, 1938 with labeling that "contain[ed] the same representations concerning the conditions of its use." 21 U.S.C. § 321(p). Sodium fluoride drops/tablets do not qualify under this clause because they were never used as a caries-preventative agent prior to June 1938. I have enclosed, as Appendix B, the entry for sodium fluoride from the 1940 Merck Index, which confirms that, while sodium fluoride was a popular rodenticide and insecticide in the 1930s, the only known medical use was as an (*externally* applied) *antiseptic*. This is further confirmed by scientific reviews of fluoride drops/tablets, which note that fluoride drops/tablets were first introduced on a limited basis in the mid-to-late 1940s, and were not regularly used until the late 1950s/early 1960s.

³ Burt BA. (1999). The case for eliminating the use of dietary fluoride supplements for young children. *Journal of Public Health Dentistry* 59(4):269-74.

⁴ E.g., Riordan PJ. (1996). The place of fluoride supplements in caries prevention today. *Australian Dental Journal* 41(5):335-42 ("[M]any people have continued to use supplements, risking dental fluorosis for no measurable benefit."); Ismail AI, et al. (2008). Fluoride supplements, dental caries and fluorosis: A literature review. *Journal of the American Dental Association* 139:1457-68 ("We believe that dentists should dismiss the misconception that there is a balance between caries and fluorosis, because patients can accrue the benefits of topical fluorides without developing fluorosis and without systemic intake."); Tomasin L, et al. (2015). The role of fluoride tablets in the prophylaxis of dental caries. A literature review. *Annali di Stomatologia* VI(1):1-5 ("Despite the fact that results discourage a systemic [fluoride] administration, this is still in use, showing low professional updating.").

2. SELLING UNAPPROVED NEW DRUGS VIOLATES *BOTH* FEDERAL AND STATE LAW

The sale of unapproved new drugs violates *both* federal and state law. On the federal level, the Food Drug & Cosmetic Act (FDCA) strictly prohibits the introduction of unapproved new drugs into interstate commerce. See 21 U.S.C. § 331(d); 21 U.S.C. § 355(a). If a corporation introduces an unapproved new drug into interstate commerce, its corporate officers may be held *criminally liable*, irrespective of whether they actually knew about or participated in the crime, so long as they had the authority to prevent the offense from occurring. 21 U.S.C. § 333(a); *United States v. Park*, 421 U.S. 658, 670-73 (1975); *United States v. Dotterweich*, 320 U.S. 277, 281-85 (1943).

On the state level, at least 17 states have statutes expressly prohibiting the sale of any drug that has not been approved by the FDA. In **California**, a state statute orders that: "No person shall sell, deliver, give away any new drug unless . . . a new drug application has been approved for it and that approval has not been withdrawn, terminated or suspended under Section 505 of the federal act (21 U.S.C. § 355)." CAL. HEALTH & SAFETY CODE § 111550.

Similarly, **Arizona** law commands that: "No person shall manufacture, sell, offer or hold for sale or give away any new drug or device unless it fully complies with the provisions of the federal act." ARIZ. ST. § 32-1962.

Illinois law commands that: "No person shall sell, deliver, offer for sale, hold for sale or give away any new drug unless (1) an application with respect thereto has been approved and the approval has not been withdrawn under Section 505 of the Federal Act, and (2) a copy of the letter of approval or approvability issued by the Federal Food and Drug Administration is on file with the Director, if the product is manufactured in the State of Illinois." 410 ILCS § 620/17.

A **New Jersey** statute commands that: "No person shall introduce or deliver for introduction into intrastate commerce in the State of New Jersey any new drug unless (1) an application with respect thereto has become effective under the Federal Act" N.J.S.A. § 24:6A-1(a).

And, in **Texas**, a state statute orders that: "A person shall not sell, deliver, offer for sale, hold for sale or give away any new drug unless: (1) an application with respect thereto has been approved and the approval has not been withdrawn under Section 505 of the federal act; and (2) a copy of the letter of approval or approvability issued by the United States Food & Drug Administration is on file with the department if the product is manufactured in this state." HEALTH & SAFETY CODE § 431.114(a).

Other states with similar prohibitions on the sale of non-FDA approved drugs include: **Colorado, Connecticut, Hawaii, Missouri, Nevada, Oregon, Pennsylvania, South Carolina, Tennessee, Virginia, Washington State, and Wyoming.**⁵

⁵ COLO. REV. ST. § 12-42.5-128; CONN. GEN. ST. § 21A-110; HAW. REV. ST. § 328-17; MO. ST. § 196.105; NEV. ST. § 585.490; ORE. REV. ST. § 689.135(13)(a); 35 PENN. ST. § 780-110; S.C. ST. §§ 39-23-70; TENN. ST. § 53-1-110; VA. ST. § 54.1-3421; WASH. ST. § 69.04.570; WYO. ST. § 35-7-118. See

3. WALGREENS IS FALSELY ASSURING CUSTOMERS THAT ITS FLUORIDE DROPS/TABLETS ARE FDA-APPROVED

Subsequent to FDA's issuance of the Warning Letter in January, I coordinated an investigation of Walgreens pharmacies to determine:

- A. If Walgreens sells fluoride drops and tablets and, if so, which brands;
- B. Whether the label or labeling⁶ for these drugs contain unapproved health claims;
- C. Whether FDA has issued any prior guidance about the approval status of the specific fluoride drugs that Walgreens is selling; and
- D. What Walgreens pharmacists are telling customers when asked about the FDA approval status of these drugs.

The investigation was carried out by myself and volunteers who visited Walgreens pharmacies near our personal areas of residence in California, New York, and Texas. This investigation confirmed the following:

A. Walgreens is selling fluoride drops and tablets. The fluoride drug products that Walgreens was selling at the stores we visited were manufactured by Sancilio & Company, Inc. ("Sancilio"), Qualitest, and Cypress Pharmaceuticals, Inc. ("Cypress").

B. The fluoride drugs at Walgreens have labels and/or labeling which contain express claims that they prevent tooth decay. The label on Sancilio fluoride drops claims they are "a dental caries preventive in pediatric patients," while the label for Qualitest's fluoride drops claims they are a "caries prophylaxis."⁷ While we were unable to obtain the label/labeling for the Cypress products, the Walgreens website asserts that Cypress fluoride tablets are a "supplement used to prevent cavities." See <http://tinyurl.com/h4nu4c3>. These health claims are materially indistinguishable from the health claims on Kirkman's fluoride drops/tablets (i.e., "dental caries preventative" and "prevention of caries"). Accordingly, per FDA's Warning Letter, the health claims being made for Sancilio, Qualitest, and Cypress products violate federal law.

C. FDA's online drug database states, in no uncertain terms, that Sancilio and Qualitest's fluoride drugs are not FDA approved. You can verify this by simply entering the NDCs⁸ for these drugs into FDA's database at <https://accessdata.fda.gov/scripts/cder/ndc/>. You can further corroborate it by entering the NDCs for these drugs into the U.S. National Library of Medicine's (NLM) online drug

also IDAHO ST. § 37-128 (prohibiting sale of non-FDA approved drugs that were not sold in state prior to 1960); KY. ST. § 217.075 (same); R.I. ST. § 21-31-16 (prohibiting sale of non-FDA approved drugs that were not sold in state prior to 1959); 18 VT. ST. § 4065 (same).

⁶ "Labeling" is defined as "all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce." 21 C.F.R. § 1.3(a). By contrast, "[l]abel means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity." 21 C.F.R. § 1.3(b).

⁷ I have enclosed the labels and labeling for these drugs, which I accessed through the National Library of Medicine's (NLM) repository for drug labeling information, as Attachments C & D.

⁸ The NDCs for Sancilio's products include 44946-1032-8 (0.5 mg/F drops) and 44946-1010-3 (1.0 mg tablets), while the NDCs for Qualitest products include 0603-1786-47 (0.5 mg/F drops). The FDA and NLM databases do not contain any NDCs for Cypress.

database at <https://dailymed.nlm.nih.gov/dailymed/>. The FDA database confirms that each of these drugs is "unapproved," and the NLM database provides the following statement for each: "This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA." (See Appendices C & D.)

D. Walgreens is (falsely) assuring its customers that these drugs are FDA approved. Despite FDA's unequivocal statements to the contrary, Walgreens pharmacists repeatedly assured the customers in our investigation that FDA has approved fluoride drops/tablets. Here, for example, are excerpts from three audiotaped conversations with Walgreens pharmacists. The first one is from a Walgreens pharmacy in El Segundo, California; the second is from a Walgreens in Cedar Park, Texas; and the third is from a Walgreens in Austin, Texas.

Excerpt No.1:

CUSTOMER: Has the FDA approved fluoride supplements? Someone told me that they weren't approved by the FDA. Do you know about that?

PHARMACIST: [Under] federal law, this requires a prescription. So they have regulated fluoride.

CUSTOMER: So these fluoride supplements would be FDA-regulated, approved by the FDA?

PHARMACIST: It has to be otherwise we can't dispense it. [Reading label: 'Dispense under a physician's order.'] That's why it's back here and you can't get it [out there].

CUSTOMER: It couldn't be sold if the FDA hadn't approved it?

PHARMACIST: It has to go thru all the FDA tests, yea. There's an approval process just like any other drug, and this one had to go through it.

CUSTOMER: Yea, cause someone had told me that [fluoride wasn't FDA approved], and I was like, that's so weird because it would have to be approved by the FDA.

PHARMACIST: It has to be.

Excerpt No.2:

CUSTOMER: Do you know if it's [fluoride] FDA-approved?

PHARMACIST: Yea, if it's a drug that we carry back here, yes ma'am.

CUSTOMER: Ok, so any prescription drug is FDA-approved?

PHARMACIST: Um-hum.

CUSTOMER: So anything here at Walgreens would be?

PHARMACIST: If it's a prescription, not necessarily everything that's out [there].

CUSTOMER: Out there. But everything's that's prescription at Walgreens would be FDA approved?

PHARMACIST: Yes, ma'am.

CUSTOMER: Ok, that's good to know.

Excerpt No. 3:

CUSTOMER: The question I have, I'm a little concerned is, it would be FDA approved?

PHARMACIST: Yes, that should be FDA approved because it's the only way we can have it here.

CUSTOMER: Oh, the only reason you can have it here is if it's FDA approved?

PHARMACIST: Yes, we cannot have anything that is not FDA approved.

CUSTOMER: Ok, and that's for all the Walgreens, everything?

PHARMACIST: Any pharmacy, not only Walgreens.

CUSTOMER: Not only Walgreens, but other pharmacies?

PHARMACIST: Otherwise it would be illegal.

CUSTOMER: Oh, ok, it's illegal if it's not FDA approved?

PHARMACIST: If it's not FDA approved.

CUSTOMER: If it's a prescription, correct?

PHARMACIST: Um-hum.

CUSTOMER: Ok, that's good to know then. Thank you.

4. WALGREENS MAY BE LIABLE FOR MISBRANDING UNDER 21 U.S.C. § 331(k)

Not only is Walgreens violating 21 U.S.C. § 331(d) by selling unapproved new drugs, but it may also be violating 21 U.S.C. § 331(k) by misbranding these drugs with impermissible health claims. As noted above, Walgreens' website claims that Cypress fluoride tablets "prevent cavities." The Walgreens website makes the same claim for fluoride drops. See <http://tinyurl.com/j8xcw6g>. Moreover, our investigation found that Walgreens pharmacists often provide customers of fluoride drops/tablets with a printout which states: "This medicine is a mineral used to help prevent cavities in children."⁹ Importantly, in *none* of these written materials does Walgreens disclose to its customers that these claims have never been approved by the FDA.

The FDCA strictly prohibits the alteration to the "labeling" of a drug, or the "doing of any other act . . . if such act is done while such article is held for sale . . . after shipment in interstate commerce and results in such article being . . . misbranded." 21 U.S.C. § 331(k). A drug is deemed "misbranded" if its labeling "is false or misleading in any particular." 21 U.S.C. § 352(a). "Labeling" is defined as "all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce." 21 C.F.R. § 1.3(a).

Under these definitions, Walgreens's act of providing its customers with Walgreens-branded documents containing impermissible health claims for the fluoride drops/tablets it sells likely constitutes misbranding under the FDCA.

5. RESEARCH SHOWS FLUORIDE DROPS/TABLETS ARE INEFFECTIVE AND DANGEROUS

As noted earlier, fluoride drops and tablets are "not generally recognized as safe and effective" for the purpose of preventing tooth decay in children, according to the FDA. FDA's conclusion is amply justified.

⁹ I have attached copies of several of the printouts we received in Appendix E.

First, fluoride drops and tablets were introduced in the 1950s/1960s on the now *universally discredited* premise that fluoride's primary benefit to teeth comes from *ingesting* fluoride while the teeth are still developing.¹⁰ The *Journal of the American Dental Association* has explained that "**fluoride incorporated during tooth development is insufficient to play a significant role in cavity protection.**"¹¹ Both the Centers for Disease Control and National Research Council have confirmed this, declaring, respectively, that "fluoride's predominant effect is posteruptive and *topical*,"¹² and "the major anticaries benefit of fluoride is *topical* and *not systemic*."¹³ In other words, fluoride works when it is applied directly to the outside of teeth (i.e. topical), not when swallowed (i.e. systemic).

This new understanding about fluoride's anti-caries mechanism eviscerates the basis for using fluoride drops and tablets, because "tablets/drops for swallowing have little to no local effect."¹⁴ Indeed, as noted in a recent review by the prestigious Cochrane Collaboration:

"Now the common view is that it is through the posteruptive (topical) effect that fluorides have caries preventative action. In this context, ingestion of the supplements is not necessary nor needed to obtain a preventive effect as the topical application of fluoride compounds is all that is required to provide preventive effect on dental caries."¹⁵

Second, whereas fluoride's predominant benefit comes from topical application, its risks arise from *ingestion*. It is well established, for example, that children who swallow fluoride drops and tablets are at significantly elevated risk of developing dental fluorosis,¹⁶ a defect of enamel that can result in embarrassing splotchy stains on a child's permanent front teeth.¹⁷ As noted in one review, "Supplement use by children younger than 5 years entails a risk of fluorosis which, at the community level, becomes a certainty."¹⁸ Based on this "clear" risk of fluorosis, and "marginal at best" benefit, even some pro-fluoride dental researchers have called for fluoride drops/tablets to be eliminated from modern medicine.¹⁹

¹⁰ Burt, *supra* note 3, at 269.

¹¹ Featherstone, JDB. (2000). The science and practice of caries prevention. *Journal of the American Dental Association* 131:891.

¹² Centers for Disease Control and Prevention. (2001). Recommendations for Using Fluoride to Prevent and Control Dental Caries in the United States. *Morbidity and Mortality Weekly Report* 50(RR14): 1-42.

¹³ National Research Council. (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. p 13.

¹⁴ Riordan PJ. (1999). Fluoride supplements for young children: an analysis of the literature focusing on benefits and risks. *Journal of Public Health Dentistry* 27:72-83, Tbl. 3. Not surprisingly, the only fluoride products FDA's OTC Monograph approves are topical products (i.e., toothpastes, rinses, gels) designed to be applied directly to the teeth. 21 C.F.R. § 355.1 *et seq.*

¹⁵ Tubert-Jeanin S, et al. (2011). Fluoride supplements (tablets, drops, lozenges or chewing gums) for preventing dental caries in children. The Cochrane Library. p. 29.

¹⁶ Ismail AI, Bandekar RR. (1999). Fluoride supplements and fluorosis: a meta-analysis. *Community Dentistry & Oral Epidemiology* 27(1):48-56.

¹⁷ Marshman Z, et al. (2008). The impact of developmental defects of enamel on young people in the UK. *Community Dentistry & Oral Epidemiology* 37:45-57.

¹⁸ Riordan, *supra* note 14, at 76,

¹⁹ Burt, *supra* note 3, at 272.

Dental fluorosis is not the only risk from early ingestion of fluoride. Fluoride exposure can also negatively impact brain development, resulting in both learning and behavioral disorders. Over 50 studies of human populations, for example, have found associations between fluoride exposure and cognitive impairment,²⁰ while over 30 laboratory experiments have confirmed—under carefully controlled conditions—that fluoride exposure can impair learning and memory capacity in rats and mice.²¹ The evidence of fluoride's interference with brain development is now sufficiently advanced that a recent review in *Lancet Neurology* classified fluoride as one of only 11 chemicals "known to cause developmental neurotoxicity in human beings."²²

Fluoride has also been classified by the prestigious National Research Council as an "endocrine disrupter" due, in large part, to its documented capacity to interfere with thyroid function, insulin production, and glucose metabolism.²³ In fact, while sodium fluoride tablets are currently used to prevent tooth decay, they were previously used by doctors as a medication to reduce thyroid function among hyperthyroid patients,²⁴ and recent research has linked fluoridated drinking water to elevated rates of hypothyroidism (under-active thyroid).²⁵ Further, studies have found that fluoride can disrupt insulin production and glucose metabolism at blood fluoride levels (~100 ppb)²⁶ comparable to those that are found in pre-school children following ingestion of 0.5 mg fluoride tablets.²⁷ There are other risks from fluoride ingestion as well, including possibly childhood cancer.²⁸

It should go without saying that a *non-FDA approved drug* with the potential to *permanently damage the brain and disrupt the endocrine system* should *not* be dispensed to *infants and toddlers* unless and until adequate and well conducted studies have been conducted and vetted by the FDA to ensure the drug's safety and effectiveness. The manufacturers of fluoride drops/tablets have had *decades* to submit these studies, but have *failed to do so*, presumably because no such studies exist.

Walgreens customers rightfully expect that the prescription drugs they purchase from Walgreens have been rigorously vetted by FDA for safety and effectiveness. This trust will be violated if Walgreens continues to sell fluoride drops and tablets with the knowledge they are not FDA approved. Alternatively, by promptly moving to remove non-FDA approved drugs from its shelves, Walgreens will demonstrate its commitment to customer safety.

²⁰ See Appendix F for a complete list of citations to these studies.

²¹ See Appendix G for a complete list of citations to these studies.

²² Grandjean P, Landrigan PJ. (2014). Neurobehavioral effects of developmental toxicity. *Lancet Neurology* 13(3):330-38, Table 2.

²³ National Research Council, *supra* note 13, at pp.224-267.

²⁴ Galletti P, Joyet G. (1958). Effect of fluorine on thyroidal iodine metabolism in hyperthyroidism. *Journal of Clinical Endocrinology* 18(10):1102-1110.

²⁵ Peckham S, et al. (2015). Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? A large observational study of GP practice data and fluoride levels in drinking water. *Journal of Community Health & Epidemiology* 69(7):619-24.

²⁶ National Research Council, *supra* note 13, at p. 264.

²⁷ Ekstrand J, et al. (1983). Plasma fluoride concentrations in pre-school children after ingestion of fluoride tablets and toothpaste. *Caries Research* 17:380, Fig. 1.

²⁸ Fluoride has been repeatedly associated with pediatric/childhood osteosarcoma. *E.g.*, Bassin EB, Wypij D, Davis RB, Mittleman MA. (2006). Age-specific fluoride exposure in drinking water and osteosarcoma (United States). *Cancer Causes and Control* 17: 421-8.

I hope, therefore, that you will take prompt action to remove all non-FDA approved fluoride drops and tablets from the list of pharmaceuticals your pharmacies dispense. Please let me know when you decide to take this action.

If I can provide any further information to facilitate your review of this matter, please do not hesitate to ask.

Yours sincerely,

A handwritten signature in black ink, appearing to read "Michael Connett". The signature is fluid and cursive, with the first name "Michael" being more prominent than the last name "Connett".

Michael Connett, Esq.
Executive Director
Fluoride Action Network
3454 Vinton Ave
Los Angeles, CA 90034
P. 802.355.0999
E. michael@fluoridealert.org

Encl: Appendices A to G

Copy: Richard Ashworth, President, Pharmacy & Retail Operations
Dwayne Pinon, Director & Managing Counsel - Pharmacy Law