FLUORIDEALERT.ORG
Fluoride Action Network

April 12, 2016

John Standley
CEO, Rite Aid Corporation
30 Hunter Lane
Camp Hill, PA 17011

Dear Mr. Standley:

The purpose of this letter is to notify you that Rite Aid 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 Rite Aid currently selling these unapproved drugs, but, as detailed below, a recent investigation found that Rite Aid 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

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 Rite Aid 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 Rite Aid. 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 Rite Aid 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 Rite Aid is acting in accord with the law.

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[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*, irrespectlve 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 approv ability 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 also* IDAHO ST. § § 37-128 (prohibiting sale of non-FDA approved drugs that were not sold in state

3. Rite Aid 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 Rite Aid pharmacies to determine:

A. If Rite Aid sells fluoride drops and tablets and, if so, which brands;
B. Whether the label or labeling[6] 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 Rite Aid is selling; and
D. What Rite Aid 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 Rite Aid pharmacies near our personal areas of residence in California, New York, North Carolina, and Vermont. This investigation confirmed the following:

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

B. The label/labeling for Sancilio fluoride products contains express claims of cavity prevention. The label and labeling for Sancilio fluoride drops and tablets make the express claim that these products are "a dental caries preventive in pediatric patients.[7] This is a materially indistinguishable claim from the one present 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 fluoride products violate federal law.

C. FDA's online drug database states, in no uncertain terms, that Sancilio's fluoride drugs are <u>not</u> FDA approved. You can verify this by simply entering the NDCs[8] 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 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.)

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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 Sancilio's drops and tablets, which I accessed through the National Library of Medicine's (NLM) repository for drug labeling information as Appendices 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).

D. Rite Aid is providing incorrect information to its customers about the FDA approval status of sodium fluoride. Despite FDA's unequivocal pronouncements that sodium fluoride drops and tablets are drugs that it has not approved for cavity prevention, Rite Aid pharmacists assured the customers in our investigation that (1) FDA has approved fluoride drops/tablets, or, alternatively, that (2) FDA approval was not required for sodium fluoride because it is a "normal mineral." Here, for example, are excerpts from three audiotaped conversations with Rite Aid pharmacists. The first one is from a Rite Aid pharmacy in Binghamton, New York; the second is from a Rite Aid in Burlington, Vermont; and the third is from a Rite Aid in Chatham, New York.

Excerpt No.1:

CUSTOMER: And are they FDA-approved, the fluoride drops? Fluoride vitamins?
PHARMACIST: I assume so, yea. That's why they're all prescription.
CUSTOMER: Ok, so they're FDA-approved for sure?
PHARMACIST: Um-hum.
CUSTOMER: Ok, thank you very much.
PHARMACIST: You're welcome.

Excerpt No.2:

CUSTOMER: Are these actual drops FDA approved?
PHARMACIST: I would, they would have to be.
CUSTOMER: They would have to be?
PHARMACIST: Because a prescription wouldn't go through when I type them.
CUSTOMER: Oh, I see
PHARMACIST: If there's a drug that's not FDA-approved, it stops me. It says, we're not going to cover this drug, because it's not FDA approved.

Excerpt No. 3:

CUSTOMER: So, I heard, one of my friends told me that this [sodium fluoride] is not an FDA approved drug. Is that true? I mean they wouldn't sell it...?
PHARMACIST: It's technically a dietary supplement.
CUSTOMER: So, it doesn't have to be FDA-approved?
PHARMACIST: No. If it was FDA approved, it would say Rx only. You need a physician's order, but it's, I mean it's, it's sodium fluoride, so it's a normal mineral.
CUSTOMER: Right, ok. So it doesn't really have to have FDA approval?
PHARMACIST: No.

Consistent with the first two excerpts, CVS pharmacists in Asheville, North Carolina and Los Angeles, California also claimed that sodium fluoride was FDA-approved for cavity prevention. The conversation in North Carolina was recorded and can be made available upon request. The conversations in Los Angeles, however, were not recorded.

4. Rite Aid May Be Liable for Misbranding Under 21 U.S.C. § 331(k)

Not only is Rite Aid 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. During our investigation, Rite Aid pharmacists provided us Rite Aid-branded printouts with drug information about sodium fluoride drops and tablets. These Rite Aid printouts uniformly claim that sodium fluoride is a "medication . . . used to prevent cavities," and that sodium fluoride "makes teeth stronger and more resistant to decay."[9] Importantly, in *none* of these written materials does Rite Aid disclose to its customers that these health 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, Rite Aid's act of providing its customers with Rite Aid-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.

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).

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

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) e fect 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]

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

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[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.

[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.

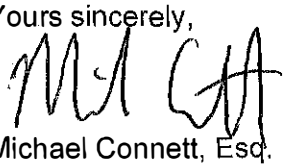
medication to reduce thyroid function among hyperthyroid patients,[24] and recent research has linked fluoridated drinking water to elevated rates of hypothyroidism (under-active thyroid).[25] Further, studies have found that fluoride can disrupt insulin production and glucose metabolism at blood fluoride 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.

Rite Aid customers rightfully expect that the prescription drugs they purchase from Rite Aid have been rigorously vetted by FDA for safety and effectiveness. This trust will be violated if Rite Aid 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, Rite Aid will demonstrate its commitment to customer safety.

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

Yours sincerely,



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Encl: Appendices A to G
Copy: Jocelyn Konrad, VP of Pharmacy
Daniel Miller, VP of Pharmacy Regulatory Affairs

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[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.