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U.S. Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Pursuant to 21 C.F.R. § 10.25(a)(2) and 21 C.F.R. § 10.30, the Fluoride Action Network and International Academy of Oral Medicine & Toxicology (collectively, "Petitioners"), respectfully submit this Petition to request that the Commissioner of the U.S. Food & Drug Administration (FDA) exercise its authority under the Food, Drug & Cosmetic Act to take action to ensure an expedited removal from the market of unapproved, unsafe, unnecessary, and ineffective sodium fluoride-containing drops, tablets, and lozenges sold for the intended purpose of caries prevention (i.e., "fluoride supplements").

TABLE OF CONTENTS

I. INTRODUCTION

On January 13, 2016, the FDA issued a Warning Letter to Kirkman Industries, Inc. ("Kirkman") in which the Agency called on Kirkman to "discontinue marketing all of the unapproved prescription drugs manufactured at [the] facility immediately." The unapproved prescription drugs at issue in this letter were sodium fluoride-containing drops and tablets sold for the labeled purpose of preventing dental caries.

In the Warning Letter, FDA stated that sodium fluoride-containing drops and tablets used for caries prevention purposes (i.e., "fluoride supplements") are "drugs" under 21 U.S.C. § 321(g), "new drugs" under 21 U.S.C. § 321(p)(1), and "unapproved new drugs" under 21 U.S.C § 355. Accordingly, because the Food Drug & Cosmetic Act (FDCA) prohibits the introduction of unapproved new drugs into interstate commerce, FDA informed Kirkman that the "marketing of these drugs . . . without an approved application constitutes a violation of the Act."

FDA's decision to take enforcement action against Kirkman for its marketing of fluoride supplements is a commendable step in the right direction, because a large body of scientific and medical evidence demonstrates that fluoride supplements are neither safe nor effective.

The FDA, however, should not limit its enforcement action against fluoride supplements to only Kirkman, as there are other, larger companies (e.g., Libertas Pharma, Inc.; Sancilo & Company, Inc.; and Qualitest) that are manufacturing and distributing identical fluoride supplements, which are being sold throughout the country by the nation's four largest pharmacies (Walgreens, CVS, Rite Aid, and Walmart). Each and every one of the issues that FDA identified with Kirkman's fluoride supplements applies with equal force to the fluoride supplements being manufactured and sold by these other

companies. The widespread sale of fluoride supplements in the U.S. thus constitutes a systematic violation of the Food Drug & Cosmetic Act.

Petitioners write today not just because manufacturers, distributors, and sellers of fluoride supplements are violating the law, but because their unlawful actions are unnecessarily placing millions of children in harm's way.

Fluoride supplements were launched in the 1940s/50s on the *universally discredited* premise that fluoride needs to be *ingested* during early childhood to provide a meaningful role in cavity prevention. The overwhelming body of evidence today shows that fluoride's predominant effect on cavities comes from *topical* application, not ingestion. Further, the decades-old studies purporting to demonstrate benefits from fluoride supplements have been universally critiqued for their low quality, highly biased study designs. Today, leading experts in the fields of dental research and health care interventions, including the prestigious Cochrane Collaboration, have concluded that fluoride supplements are neither necessary nor effective, particularly in the current context of widespread exposures to fluoride toothpaste and topical fluorides. In short, fluoride supplements have become a useless relic of a discredited paradigm.

Fluoride supplements are not just ineffective, they are dangerous. A large body of science demonstrates that fluoride is a developmental neurotoxin and endocrine disrupting agent, whose ingestion during childhood poses serious potential risks to brain development and thyroid health, as well as other harm, including dental fluorosis, bone fragility, osteosarcoma, and impaired glucose metabolism.

The problem today is not *under*-exposure to fluoride, but *over*-exposure. Recent national survey data collected by the U.S. Centers for Disease Control shows that between 41% and 64% of adolescents now have dental fluorosis, with 4% to 29% of adolescents having *advanced* forms of this condition. Dental fluorosis is a visible mineralization defect of tooth enamel caused by excessive fluoride intake, which can be disfiguring when present on a child's front teeth.

Fluoride supplements remain a significant cause of the over-exposure problem in the U.S. Studies have repeatedly demonstrated that inappropriate prescription of fluoride supplements is a widespread and persistent problem in the U.S., with many children being prescribed these drugs despite having high background exposure to other sources of fluoride, including fluoridated water and fluoride toothpaste. Such poorly monitored, highly variable exposures to a neurotoxic, endocrine disrupting agent, is a recipe for long-term disaster that demands decisive action now.

Rather than continuing to supplement children's intake of fluoride, the urgent need now is to find ways to *reduce* fluoride exposure. Eliminating *unapproved* fluoride drugs from the market is the most obvious place for FDA to start. The dangers posed by these drugs, coupled with their ineffectiveness, deceptive marketing practices, misbranding violations, and undermining effect on FDA's OTC Monograph on fluoride, make fluoride supplements a high priority drug for FDA enforcement actions per the considerations set forth in the Agency's Compliance Policy Guide for Marketed Unapproved Drugs.

II. ACTION REQUESTED

Petitioners request that the Commissioner issue a notice of the FDA's intent to take enforcement actions (including seizures, injunctions, civil penalties, and/or criminal sanctions) against any and all companies that manufacture, distribute, and/or otherwise introduce into interstate commerce unapproved sodium fluoride-containing drops, tablets, and lozenges that are sold for the intended purpose of caries prevention (i.e., "fluoride supplements").

III. STATEMENT OF GROUNDS

A. FLUORIDE "SUPPLEMENTS" ARE UNAPPROVED NEW DRUGS

In its Warning Letter to Kirkman, the FDA confirmed that fluoride supplements are "drugs" under 21 U.S.C. § 321(g), "new drugs" under 21 U.S.C. § 321(p)(1), and have never been approved as safe and effective under 21 U.S.C. § 355.[1] Introducing fluoride supplements into interstate commerce, therefore, violates the Food Drug & Cosmetic Act (FDCA), as the FDCA plainly prohibits the sale of unapproved new drugs. 21 U.S.C § 331(d); 21 U.S.C. § 355(a).

Kirkman has challenged FDA's conclusion that fluoride supplements are "new drugs" under 21 U.S.C. § 321(p)(1), based on Kirkman's contention that fluoride supplements are "generally recognized as safe and effective."[2] Kirkman's argument, however, is at odds with both law and science. As set forth herein, FDA's conclusion that fluoride supplements are "new drugs" is factually, legally, logically, and scientifically unassailable.

1. Fluoride Is a "Drug" When Used for Caries Prevention

The FDA has consistently classified fluoride as a "drug" when used to treat or prevent disease, including the disease of tooth decay ("caries").[3] FDA's classification of fluoride as a drug is in clear harmony with the FDCA, which defines drugs, *inter alia*, as articles "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." 21 U.S.C. § 321(g).

2. Fluoride Supplements Are "New Drugs" When Sold for Caries Prevention

As set forth in 21 U.S.C. § 331(d), the FDCA prohibits the sale of "new drugs" that have not been approved as safe and effective by FDA per the rigorous requirements of 21 U.S.C. § 355. A "new drug" is "any drug," except those that meet the following two "very narrow"[4] exceptions: (1) It was on the market prior to June 25, 1938 with the same "labeling" and "representations concerning the conditions of its use," and/or (2) it is "generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective under the conditions prescribed, recommended, or suggested in the labeling." 21 U.S.C. § 321(p)(1).

For the following reasons, fluoride supplements do not meet either of these "very narrow" exceptions.

a. Fluoride Supplements Were Not on the Market Prior to June 1938

Sodium fluoride was never used prior to June 1938 as a caries preventive agent, let alone with the same labeling and recommended conditions for use as sodium fluoride drugs that are now on the market. Prior to 1938, sodium fluoride was commonly used as a roach and rodent poison, but its use in American *medicine* was virtually unknown, with the exception of a rare use as an *externally applied* antiseptic and antiperiodic.[5] Importantly, sodium fluoride had no use in *dentistry*, let alone as an agent to be *swallowed* by children for caries prevention. This is confirmed by the 1940 edition of the Merck Index, which is attached as Exhibit 5, as well as the 1938 and 1940 editions of the United States Pharmacopeia, which are attached as Exhibits 7 and 8. This fact is further confirmed by scientific reviews of the fluoride supplement literature, which unanimously state that fluoride supplements were introduced no earlier than the mid-1940s, and were not widely used until the late 1950s or early 1960s.[6]

b. Fluoride Supplements Are Not Generally Recognized as Safe & Effective (GRASE)

In its January 13, 2016 Warning Letter to Kirkman Industries, Inc. ("Kirkman"), FDA stated its position that Kirkman's fluoride supplements "are not generally recognized as safe and effective under the conditions prescribed, recommended, or suggested in their labeling." Importantly, the only labeling information from Kirkman's fluoride supplements that FDA identified in its Warning Letter is the claim that these supplements are an "aid in the prevention of dental caries." Accordingly, FDA's conclusion that Kirkman's supplements are not generally recognized as safe and effective (GRASE) applies equally to *all* fluoride supplements with labeling that makes caries prevention claims.[7]

FDA's conclusion that fluoride supplements are not GRASE for caries prevention is abundantly supported by both (A) the case law defining GRASE, and (b) the scientific literature on fluoride supplements. We begin first with a summary of the case law, before proceeding to a discussion of the science.

i. The Legal Standard for Determining GRASE

The U.S. Supreme Court has made clear that the standard for proving GRASE is a "rigorous one," which is equally as stringent as the standard FDA uses for assessing a New Drug Application (NDA) under 21 U.S.C. § 355. *Weinberger v. Hynson, Westcott & Dunning, Inc*., 412 U.S. 609, 629-30 (1973). Under both the GRASE and NDA inquiries, there must be "substantial evidence" of safety and effectiveness, which includes "adequate tests by all methods reasonably applicable" to demonstrate safety, and "adequate and well-controlled investigations" to demonstrate effectiveness. 21 U.S.C. § 355(d); 21 C.F.R. § 314.126; *Weinberger v. Bentex Pharms., Inc*., 412 U.S. 645, 653 (1973) ("[T]he reach of scientific inquiry under both [21 U.S.C. § 355] and [21 U.S.C. § 321(p)] is precisely the same."). Accordingly, "to qualify as GRASE, a drug must meet the same elaborate, technical, scientific testing requirements that it would have to meet to win approval as a 'new drug.'" *United States v. 50 Boxes*, 909 F.2d 24, 26 (1st Cir. 1990).

Under the rigorous GRASE standard, it is immaterial if physicians "believe" that a drug works, or if poorly-conducted studies indicate a benefit, because the "clinical impressions of practicing physicians and poorly controlled experiments do not constitute

an adequate basis for establishing efficacy." *Weinberger*, 412 U.S. at 630. Even when there is an "expert consensus" that a drug is safe and effective, the consensus does not constitute GRASE if it is not based on adequate and well controlled studies that independently satisfy the requirements of 21 U.S.C. § 355. *See id.* at 632 ("[A] drug can be 'generally recognized' by experts as effective for intended use within the meaning of the Act *only* when that expert consensus is founded upon 'substantial evidence' as defined in [21 U.S.C. 355]." (emphasis added)).[8]

Whereas expert consensus is not sufficient, without more, to establish a drug's status as GRASE, a *dispute* among experts *is* sufficient, without more, to preclude a drug's classification as GRASE. *Premo Pharm. Labs., Inc. v. United States*, 629 F.2d 795, 803 (2d Cir. 1980) ("[A] genuine dispute among qualified experts regarding a drug product's safety and effectiveness preclude[s] its qualifying for exclusion as 'generally recognized.'"); *accord United States v. Articles of Drug for Veterinary Use*, 50 F.3d 497, 501 (8th Cir. 1995); *Tri-Bio Labs., Inc. v. United States*, 836 F.2d 135, 141 (3d Cir. 1987).

Based on the "very narrow"[9] grounds on which drugs can qualify as GRASE, the FDA has stated that, although "theoretically possible," "it is *not likely* that *any* currently marketed prescription drug" satisfies the GRASE exception.[10]

ii. The Science on Fluoride Supplements

It is quickly apparent upon reviewing the scientific literature on fluoride supplements that these drugs are *not* generally recognized as safe and effective by experts in the field, particularly under modern conditions where the vast majority of children are receiving fluoride from many other sources besides water, such as toothpaste and processed beverages made with fluoridated water.

The existing state of scientific research on fluoride supplements permits the following conclusions, each of which undermines the claim that fluoride supplements qualify as GRASE:

a) <u>There Are No Studies Demonstrating the Safety of Fluoride Supplement Use</u>

In order to qualify as GRASE, there must be "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling." 21 U.S.C. § 355(d)(1). In the case of fluoride supplements, such studies *do not exist*.

In a recent systematic review of randomized and quasi-randomized trials on fluoride supplements, the Cochrane Collaboration was unable to locate a single qualifying study that investigated adverse effects other than dental fluorosis, and even with fluorosis, the Cochrane Collaboration could only locate a single study.[11] According to the Cochrane Collaboration review, "No data were available concerning adverse effects related to fluoride supplementation in children aged less than 6 years. The ratio benefit/risk of fluoride supplementation was thus unknown for young children."[12]

Fluoride has recently been classified as a developmental neurotoxin that can harm cognitive abilities like learning and memory;[13] an endocrine disruptor that can impair thyroid and insulin function;[14] and is widely recognized as a bone-seeking element that

can weaken bone[15] and plausibly induce osteosarcoma.[16] As discussed below, there is compelling reason to believe that fluoride supplements may cause some or all of these harms.[17] Yet, as the Cochrane review has revealed, not a single one of these risks, or any other non-dental risk associated with fluoride ingestion, has ever been investigated in a randomized or quasi-randomized trial of fluoride supplements. On this basis alone, fluoride supplements lack the substantial evidence of safety that is necessary for establishing GRASE, per 21 U.S.C. § 355(d)(1).

b) Fluoride Supplements Cause Dental Fluorosis

A drug cannot be classified as GRASE if adequate tests "show that the drug is unsafe for use" under the recommended conditions of use. 21 U.S.C. § 355(d)(2). As noted above, there have been no randomized trials investigating the *non-dental* effects of fluoride supplements, but there has been a randomized trial, as well as many cross-sectional and case-control studies, investigating the relationship between fluoride supplement use and dental fluorosis. These studies have consistently indicated that supplement use causes fluorosis, including in its "mild to moderate" forms.[18] 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."[19]

Fluorosis is a mineralization defect of tooth enamel that is likely caused by fluoride's interference with tooth-forming cells.[20] It is evident, therefore, that fluoride supplements induce physiological changes in the body that go beyond cavity prevention,[21] and it is biologically plausible that cells in other tissues, including the pinealocytes in the pineal gland, can be affected at the same doses that impair enamel-forming cells.[22] In fact, among the very few (non-randomized) studies to consider the non-dental effects of fluoride supplements, a range of systemic effects have been observed, including headaches, listlessness, gastric distress, weakness, skin rashes, wheezing, and reductions in alkaline phosphatase activity.[23]

Further, the CDC has recognized[24]—and research has repeatedly demonstrated[25]—that the tooth staining caused by both "mild" and "moderate" fluorosis are "esthetically objectionable" conditions when present on the front teeth. Although this staining is sometimes dismissed as a mere "cosmetic effect," research has found that esthetically objectionable staining on the front teeth, including the white splotches and streaks produced by fluorosis, can cause significant embarrassment and social anxiety for growing adolescents,[26] which can have damaging consequences for self-esteem and mental well-being.[27] In fact, after reviewing photographs of dental fluorosis, a National Institute of Mental Health panel concluded that "individuals who have suffered impaired dental appearance as the result of moderate to severe (dental) fluorosis are probably at increased risk for psychological and behavioral problems or difficulties."[28]

Since studies clearly show that fluoride supplements cause dental fluorosis when used under the recommended conditions, the results of existing supplement studies—even though profoundly limited in scope—negate the status of supplements as GRASE under 21 U.S.C. § 355(d)(2).

c) Effectiveness of Supplements Is "Marginal at Best" and Based on Weak, Outdated, and Inconsistent Science

Fluoride supplements were introduced in the 1940/50s on the now *universally discredited* premise that fluoride's predominant benefit to teeth comes from *ingesting* an "optimal" dose of fluoride during the *preeruptive* stage of tooth development.[29] As explained in the *Journal of the American Dental Association*, "fluoride incorporated during tooth development is insufficient to play a significant role in cavity protection."[30] Both the Centers for Disease Control and National Research Council have confirmed this, declaring, respectively, that "fluoride's predominant effect is *post*eruptive and *topical*,"[31] and "the major anticaries benefit of fluoride is *topical* and *not systemic*."[32] In other words, fluoride works when it is applied directly to the outside of erupted teeth (i.e. topical), not when swallowed (i.e. systemic). This paradigmatic shift[33] in our understanding of fluoride's cariostatic mechanism largely eviscerates the basis for fluoride supplements (i.e., *ingesting* an "*optimal*" dose of fluoride). As noted in one expert review:

> There was a time when ingestion of fluoride in the range of 0.05 to 0.07 mg F/kg body weight/day was considered 'optimal' for preeruptive caries prevention. In light of present knowledge that preeruptive fluoride has little preventive effect, this range has better application as an estimate of the maximum amount to be ingested by young children if fluorosis is to be kept at its lowest level.[34]

The Cochrane Collaboration has seconded this assessment, noting:

> 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.[35]

Further, it bears emphasizing that most of the studies purporting to demonstrate the effectiveness of fluoride supplements are methodologically flawed studies[36] that were conducted at a time when fluoride toothpastes, and other topical fluorides, were not widely used.[37] Modern reviews of the supplement literature have questioned, therefore, whether supplements will have any demonstrable benefits if investigated with methodologically sound study designs in the current context of widespread background exposure to topical fluoride products and other fluoride sources.[38]

This expert skepticism about the effectiveness of fluoride supplements gains empirical support from a series of studies published since 1990 which have failed to find any caries preventative benefit at all.[39] The evidence of effectiveness has thus been characterized as "very thin,"[40] "weak,"[41] "low,"[42] and "inconsistent."[43] The evidence of effectiveness of supplements is particularly weak for infants and toddlers.[44] And, although the American Dental Association now only recommends fluoride supplements for children with "high caries-risk,"[45] the effectiveness of supplements for high caries-risk

children is "unknown."[46] In fact, several recent studies, including a two-year double blind trial, have failed to find any benefit of supplements in high caries-risk populations.[47]

The following are some observations from the scientific literature on the effectiveness of supplements that address the aforementioned issues. We begin first with comments on the methodological flaws in most of the supplement studies:

> "Like most recent dental or medical systematic reviews, our review also demonstrated that the majority of the studies were highly biased."[48]

> "The basis for the widespread acceptance of fluoride supplements in caries prevention is a large number of mostly small clinical trials in the late 1950's and 1960's. The early studies have been reviewed again recently in a series of publications and they have again been criticized. The criticisms are serious and virtually none of the early fluoride supplement studies would be published today, because of methodological and other shortcomings."[49]

> "There are always aspects of study design and methods in clinical trials that can be criticized. Sometimes, the flaws do not compromise the validity of the findings, but it would appear that the way many early clinical trials of fluoride supplements were performed undermines their conclusions. In mitigation, it can be conceded that epidemiology was not so well developed as a science in the 1960s and 1970s, analytical methods were similarly poorly understood, and today's easy access to computers did not exist. These explanations may excuse the fact that the early studies were done, but they do not excuse us today if we base policy on these studies."[50]

> "The design of these early studies did not follow the now accepted protocol calling for random allocation, blind examinations, and use of standard criteria for diagnosis of caries. They also included a small number of children and the majority of their findings could be used to provide support for the topical effect of fluoride supplements as well as systemic effects. Overall, these early findings can only be treated as 'indications for further investigation.'"[51]

> "The quality of the trials included in this review was generally low and many reports lacked important data or methodological information. This is probably due to the fact that most of the studies were relatively old."[52]

> "Few studies with good quality were identified in general. Only 3 out of 779 studies were acceptable."[53]

The following are observations about the ineffectiveness of prescribing fluoride supplements in an age of widespread topical fluoride use:

> "The additional reductions in dental caries to be achieved from using fluoride supplements, on top of what we already have from fluoride in drinking water, toothpaste, professional dental products, mouthrinses, and uncontrolled amounts in foods and beverages, has to be ***marginal at best***. On the other hand, the risk of fluorosis from the use of supplements is clear."[54]

> "it is unlikely that supplements could offer a benefit that is not achievable [by] regular use of fluoridated toothpaste, and children unwilling to use toothpaste regularly are unlikely to eat supplements regularly."[55]

Based on these and other considerations, the Cochrane Collaboration has concluded:

> "There is thus a lack of evidence from the review to make actual good recommendations. Today, the effect of fluoride supplements in children using fluoride toothpastes on a regular basis would probably be limited."[56]

It bears emphasizing that the Cochrane Collaboration is the one of the world's most pre-eminent research bodies for investigating the effectiveness of health care interventions. It's conclusion, therefore, that there is a "lack of evidence" to make "actual good recommendations" about the effectiveness of supplements in caries prevention today is fatal to the notion that supplements are generally recognized as effective "*among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs*." 21 U.S.C. § 321(p)(1).

d) Many Experts Disagree that Fluoride Supplements Are Safe and Effective

As noted earlier, federal courts have held that "a *genuine dispute* among qualified experts regarding a drug product's safety and effectiveness *preclude[s]* its qualifying for exclusion as 'generally recognized." *Premo Pharm.*, 629 F.2d at 803 (emphases added); *accord Articles of Drug for Veterinary Use*, 50 F.3d at 501;*Tri-Bio Labs.*, 836 F.2d at 141. This rule of law is again fatal to a determination of fluoride supplements as GRASE, for as indicated above, and as further explained herein, many experts have rejected the premise that fluoride supplements are safe and effective, particularly under modern conditions of high background exposures to fluoride.

While some expert reviewers continue to recommend the use of fluoride supplements,[57] others have called for their complete elimination.[58] This split in expert opinion was recognized in a recent publication, which noted that: "Lack of consensus exists among researchers: some support the retention of the existing fluoride schedule, while others feel strongly about reducing or completely eliminating the fluoride supplement as a caries prevention agent."[59]

A number of experts have concluded that the risks of fluoride supplements outweigh the benefits,[60] or that there is too much uncertainty to reach firm conclusions. The following

are representative conclusions from these experts:

> "The case is essentially a risk-benefit issue – fluoride has little preeruptive impact on caries prevention, but presents a clear risk of fluorosis. Fluoride supplements, when ingested for a preeruptive effect by infants and young children in the United States, therefore, now carry more risk than benefit."[61]
>
> "Comparing risks and benefits, the balance is against the use of [fluoride supplements] because, as said before, [ingested] fluoride has little effect on caries prevention but involves an evident risk for dental fluorosis."[62]
>
> "[T]he weight of recent evidence clearly suggests that the risks from dietary fluoride supplements may outweigh the benefits."[63]
>
> "Based on these results, it may not be appropriate to recommend the ingestion of fluoride supplements in children under 6 years as there is considerable uncertainty surrounding the ratio benefit/risk of this preventive intervention."[64]

The fact that experts are rejecting the notion that fluoride supplements are safe and effective precludes the conclusion that fluoride supplements are GRASE, because it establishes—*at a minimum*—that a genuine dispute exists among experts, even among experts who have not considered other possible adverse effects of fluoride besides fluorosis.

e) Experts Disagree About the Safety and Effectiveness of Fluoride Supplements *Under the Conditions Recommended and Prescribed*

Finally, in order for a drug to be GRASE, the drug must be generally recognized as safe and effective "*for use under the conditions prescribed, recommended, or suggested in the labeling thereof.*" 21 U.S.C. § 321(p)(1). This consideration provides a separate and independent basis for precluding GRASE status for fluoride supplements, because there are experts who, while not overtly calling for an elimination of fluoride supplements altogether, have sharply questioned the therapeutic necessity of fluoride supplementation and/or the very crude guidelines upon which the dosage is determined.

As noted earlier, the very purpose for which fluoride supplements are prescribed (i.e., ensuring that children ingest a purported "optimal" daily intake of fluoride) has been sharply questioned in recent years, based on the lack of meaningful benefit from *swallowing* fluoride. As one study recently concluded:

> "[A]chieving a caries-free status may have relatively little to do with fluoride intake, while fluorosis is clearly dependent on fluoride intake. . . . Thus, given that the present study found considerable overlap among caries/fluorosis groups in terms of mean fluoride intake and extreme variability in

> individual fluoride intakes for those with no fluorosis or caries history, firmly recommending an 'optimal' fluoride intake is problematic, and as stated by Burt and Eklund, perhaps it is time that 'the term optimal fluoride intake be dropped from common usage."[65]

But, even if there is an "optimal" intake of fluoride, experts have criticized the dosing instructions for fluoride supplements as recklessly simplistic and crude. First, the labeling for fluoride supplements bases the dose on age, without any consideration of a child's bodyweight,[66] thus creating substantial variation in the actual dosage (mg/kg/day) that children receive.[67] As noted by one expert in the field:

> "Although it is reasonable to expect the risk of fluorosis in children to be a function of dose per unit mass, the [fluoride supplement] schedule is age-based rather than body mass based. This is probably for reasons of expediency, but such a schedule, recommended for all children who live in non-fluoridated areas, should be very cautious because at a population level many children are not of average mass for age. . . . Children who are small or light for their age occur in the population with a predictable frequency and recommendations should allow for this."[68]

Second, no consideration is given in the labeling on many fluoride supplements to the many other non-water sources of fluoride (e.g., toothpaste) that children now receive,[69] which can easily exceed the purported "optimal" intake. This is a striking omission, since "[v]irtually all authors have noted that some children could ingest more fluoride from [toothpaste] alone than is recommended as a total daily fluoride ingestion."[70] Here are some representative concerns from the literature:

> "If fluoride supplements are to be used, then accurate information on not only fluoride content of the residential water source, but on background levels of fluoride intake from food and beverages, type of feeding, kind of water used in reconstituting foods and beverages, use of beverages versus water at home or at child care, the possibility of a diffusion effect, and the use and ingestion of dentrifice and even mouthrinses and gels may need to be considered in making recommendations for appropriate dosages of fluoride supplements in children. These complex sets of data are difficult to obtain even on a research basis, much less in daily dental and medical practice."[71]

> "[P]recisely estimating total fluoride intake is quite difficult in research studies and clearly not feasible in clinical practices. Substantial fluoride intake from a single source (for example, dentrifice, supplements, water, juice) could put a child at high risk, even when intake from all other sources is moderate or low."[72]

> "The complexity of the contribution of diet, drinks, and fluoride supplements and dentrifices to the total fluoride intake is evident from these studies. No single dosage schedule can account for the individual variation in fluoride intake by infants and children . . . ."[73]

Even the organizations that created the fluoride supplement dosing schedule (i.e., American Dental Association, American Academy of Pediatrics, and American Academy of Pediatric Dentistry) have stated that "All sources of fluoride must be considered, including primary drinking water, other sources of water, prescriptions from the dentist, fluoride mouthrinse in school, and fluoride varnish."[74] Despite this, the conditions of recommended use for fluoride supplements, as set forth on the labeling of many fluoride supplements, make no reference to any non-water sources of fluoride,[75] and those that do reference non-water sources only refer to a single source (toothpaste).[76]

In short, the scientific literature demonstrates a sharp disagreement among experts about the safety and effectiveness of "*the conditions prescribed, recommended, or suggested in the labeling*" of fluoride supplements (i.e., recommending the dose based solely on the child's age and fluoride level in water) to achieve the dubious goal of providing an "optimal" fluoride intake for caries prevention.

3. Fluoride Supplements Are Not Subject to Ongoing DESI Proceedings

Petitioners recognize that FDA allows unapproved new drugs to remain on the market if they are subject to ongoing Drug Efficacy Study Implementation (DESI) proceedings. This cannot, however, be the basis for allowing fluoride supplements to remain on the market because the one and only DESI review of a fluoride supplement (i.e., Enziflur) was conducted and completed in the 1960s.

As the FDA explains in its Compliance Policy Guide, DESI reviews are *only* conducted on drugs that were approved as safe by the FDA between 1938 and 1962, as well those drugs that are identical, related, or similar (IRS).[77] It is a matter of historical fact that the only fluoride supplement that FDA approved as safe between 1938 and 1962 was a calcium fluoride-vitamin combination called Enziflur.[78] It is also a matter of historical fact that the National Research Council (NRC) completed its DESI review of Enziflur in 1969,[79] and that, as a result of NRC's unfavorable findings on Enziflur's efficacy, the FDA withdrew its approval of Enzilfur and all IRS drugs in the 1970s.[80] Accordingly, the one fluoride supplement that had been approved as safe between 1938 and 1962, and all IRS drugs thereto, have already been subjected to a DESI proceeding. There are, therefore, no "ongoing" DESI proceedings on fluoride supplements.

Further, although NRC's conclusion regarding Enziflur was based on the lack of evidence that vitamins enhance the effectiveness of fluoride as well as Enziflur's cumbersome dosage formulation,[81] this does not mean that NRC's DESI review established the effectiveness of fluoride. The DESI case file for Enziflur shows precisely what references the NRC reviewed in considering the effectiveness of Enziflur.[82] NRC summarized these references as follows: "None of the references cited contains data from controlled clinical investigations showing that this product is effective regarding any of the claims made on the package or in the descriptive literature."[83] While this does not mean that the NRC concluded that fluoride itself is ineffective, it does mean that NRC's review was not designed nor conducted to answer that question.[84]

B. Enforcement Action Against Fluoride Supplements Is Abundantly Justified Under FDA's Compliance Policy Guide Factors

The requested action that Petitioners seek is amply justified by the factors FDA considers for prioritizing which unapproved marketed drugs to target with enforcement actions. Indeed, FDA's decision to take enforcement action against Kirkman for its marketing of fluoride supplements demonstrates *ipso facto* the Agency's own recognition that fluoride supplements warrant FDA action.

As set forth in FDA's Compliance Policy Guide for Marketed Unapproved Drugs, the Agency prioritizes enforcement actions against unapproved new drugs that fit one or more of the following categories:

1. Drugs with potential safety risks;
2. Drugs that lack evidence of effectiveness;
3. Health fraud drugs;
4. Drugs that present direct challenges to the new drug approval and OTC drug monograph systems;
5. Unapproved new drugs that are also violative of the Act in other ways;
6. Drugs that are reformulated to evade an FDA enforcement action.[85]

For the following reasons, fluoride supplements fit not just one, but *five* of these categories, thus justifying prompt action against these drugs.

1. Fluoride Supplements Have Serious Potential Safety Risks

As discussed earlier, it is already well proven that fluoride supplements cause dental fluorosis in a substantial number of children.[86] Further, although there has never been a randomized or quasi-randomized trial to investigate the *non-dental* effects of fluoride supplements, isolated studies and case reports have reported a range of side effects from fluoride supplementation, including headaches, listlessness, gastric distress, weakness, skin rashes, and wheezing.[87] The most serious potential risks from fluoride exposure, however, have never before been investigated in any supplement study, including short- and long-term harm to the nervous, endocrine, and skeletal systems. As discussed herein, there are compelling reasons to believe that fluoride supplementation may cause and/or contribute to these harms.

a. General Considerations

Before addressing the specific potential risks of fluoride suppelmentation, we begin with three important considerations that bear on each and every one of these risks.

First, surveys spanning more than three decades have repeatedly documented that many doctors and dentists inappropriately prescribe fluoride supplements to children with high background exposures to fluoride, including children living in fluoridated areas,[88] and children ingesting high levels of fluoride from other sources, including fluoridated toothpaste.[89] Since this problem has proven to be both widespread and "persistent,"[90] any assessment of the safety of fluoride supplements needs to account for the very real, predictable, and foreseeable scenario in which children are consuming fluoride supplements *in addition to* fluoridated water, fluoridated toothpaste, and other

significant sources of fluoride, including processed beverages and foods contaminated with fluoridated water, fluoride pesticides, and fluoride-rich bone particles.[91]

Second, as with any other drug and toxic substance, there is a wide range of sensitivity in how individuals respond to fluoride, with some people being tolerant to large doses, and some people being sensitive to small ones.[92] The research on fluoride demonstrates that certain factors can greatly increase one's susceptibility to suffering harm. Factors that increase susceptibility to fluoride toxicity include: suboptimal nutrient intake;[93] genetics;[94] renal disease;[95] diabetes;[96] and elevated lead exposure.[97] Several of these factors, including suboptimal nutrient intake[98] and elevated lead exposure,[99] are more likely to occur among low-income communities, and it should therefore be anticipated that low-income communities will generally be more vulnerable to harms caused by any form of fluoride supplementation. This point has important implications because the American Dental Association, and other proponents of fluoride supplements, now recommend that fluoride supplements be targeted to children at "high caries risk,"[100] which will invariably increase the proportion of low-income children receiving these drugs due to the strong link between poverty and tooth decay.[101]

Finally, in considering the potential safety risks of fluoride exposure, consideration must be given to recent data showing unprecedentedly high levels of dental fluorosis in the U.S. population. The National Health and Nutrition Examination Survey (NHANES) in 1999-2004 found that 41% of U.S. adolescents had dental fluorosis, including approximately 3.6% with moderate and severe forms of the condition.[102] These rates are far higher than the rates that existed when fluoride supplements were first introduced in the 1940s/50s.[103] But the problem has gotten even worse, as the most recent NHANES survey (from 2011-2012) found that 64% of adolescents had fluorosis, with an astounding 27% having moderate fluorosis, and an additional 2% having severe fluorosis.[104]

It is against this backdrop of widespread overexposure to fluoride, high individual variability to fluoride, and persistent inappropriate prescriptions of fluoride supplements, that the FDA should assess the potential safety risks posed by fluoride supplements. We turn now to a discussion of these risks.

b. Developmental Neurotoxicity

Fluoride has recently been classified as one of only 11 chemicals "known to cause developmental neurotoxicity in human beings."[105] Developmental neurotoxicity associated with fluoride exposure has been demonstrated in both human and animal populations, and is reflected by problems in learning,[106] memory,[107] and behavior.[108] The research, which almost exclusively post-dates 1990, is substantial. It includes over 50 studies associating fluoride exposures with impaired cognitive performance in humans, as determined through IQ tests,[109] the Rey-Osterrieth complex figure test,[110] and the neurobehavioral core test battery (NCBT),[111] as well as over 30 studies finding that fluoride exposure impairs the learning and/or memory capacity of rodents.[112] Many of the IQ studies have observed IQ reductions among children drinking just 1.5 to 3 mg/L fluoride in the water, which is only modestly more fluoride than is added to U.S. water systems.[113] This is a particularly narrow margin for American children living in fluoridated areas who use fluoride toothpaste because fluoride toothpaste is not yet widely available in rural Chinese communities, which is where most of the fluoride/IQ studies have been conducted.[114]

The potential for neurological harm from fluoride supplements is further indicated by the fact that pre-school children ingesting 0.5 mg fluoride tablets have daily spikes in their blood fluoride levels (*average* = 85 ppb)[115] that exceed the levels associated with behavioral alterations in rats consuming fluoride for 6 months (77 ppb).[116] Although these spikes are short-lived (i.e., 30 to 60 minutes), their daily occurrence during the first 6 six years of a child's life raises significant cause for concern.

While the neurological effects of fluoride have never been the subject of a randomized trial, one of the only trials on fluoride supplements to monitor side effects reported "neurological" symptoms (e.g., headaches, listlessness, and weakness) among a small subset of children receiving the supplements.[117] This study was published prior to the current understanding that fluoride is a developmental neurotoxin, but should be interpreted in the context of what is now known about fluoride and the brain.

Based on this research, developmental neurotoxicity must be considered a potential safety risk for infants, toddlers, and young children who receive daily fluoride supplements.

c. Thyroid Disorders

Fluoride is classified by the National Research Council as an "endocrine disrupter" due, in large part, to its documented capacity to interfere with thyroid function, particularly in those with suboptimal intakes of iodine.[118] In fact, while sodium fluoride tablets are now used to prevent tooth decay, they were previously used by doctors in Europe as a medication to reduce thyroid function among adult hyperthyroid patients.[119] In one clinical trial, daily intake of 4 to 6 mg of fluoride, in the form of sodium fluoride tablets, was sufficient to reduce the basal metabolism rate within 2 to 5 months. When accounting for the difference in bodyweight between these *adult* patients and the *children* taking sodium fluoride for caries prevention, the daily dosage (mg/kg/day) of the two treatments is similar (i.e., within a factor of two to three).[120] Moreover, whereas sodium fluoride was only given for less than 5 months in the hyperthyroidism trial, children are given sodium fluoride for caries prevention for up to 16 years. The implications of such long-lasting, early-life exposure to thyroid health has never been the subject of study.[121]

Recent research has reported a significant association between fluoride in drinking water and hypothyroidism,[122] further suggesting that fluoride's ability to lower thyroid function is not limited to those with overly active glands. The potential for childhood sodium fluoride treatment to disrupt thyroid function, therefore, must be taken seriously, particularly for children with suboptimal intakes of iodine.[123]

c. Impaired Glucose Metabolism

Studies on both humans and animals have repeatedly found that excessive fluoride intake impairs glucose metabolism, resulting in elevated blood glucose levels.[124] The mechanism by which fluoride causes this effect remains the subject of ongoing study, with some researchers suggesting that it involves an inhibition of insulin production and/or an increase in insulin resistance. In 2006, the National Research Council reviewed much of this literature,[125] and concluded:

> "The conclusion from the available studies is that sufficient fluoride exposure appears to bring about increases in blood glucose or impaired glucose tolerance in some individuals and to increase the severity of some types of diabetes."[126]

As the NRC noted, existing studies indicate that fluoride's impairment of glucose metabolism occurs when the blood fluoride level exceeds 100 ppb.[127] This raises significant questions about the safety of fluoride supplementation, because the ingestion of just 0.5 mg fluoride causes spikes in blood fluoride levels to equal or exceed 100 ppb in preschool children.[128] In fact, based on fluoride's effects on glucose metablism, some researchers have recommended that diabetic children use low-fluoride toothpastes:

> "[K]nowing that chronic [fluoride] intake is capable of decreasing insulin signal and causing insulin resistance, the use of dentifrices with lower F content is recommended, especially for diabetic children, for whom excessive F consumption may lead to health implications."[129]

This recommendation applies with even greater force to fluoride supplements, since ingestion of toothpaste is inadvertent, but ingestion of supplements is *by design.*

d. Bone Fragility

The bone is the principal site of fluoride accumulation in the body, and the rate of accumulation is particularly high during infancy and early years of life.[130] There is little dispute that fluoride accumulation reduces the strength of bone;[131] the only question is what dose, and under what conditions, this deterioration occurs. The NRC has concluded that consumption of water with $\geq$4 ppm fluoride in water increases the risk of fracture,[132] and that there is "suggestive" evidence of an increased fracture risk among people consuming water with $\geq$ 2 ppm.[133] However, virtually all published research on fluoride and bone fracture has focused on adult populations; there is very little information on the impact of early-life fluoride exposures, including fluoride supplementation. One of the few studies to investigate the relationship between fluoride and bone fracture in children, found a significant relationship between the presence of dental fluorosis and prior history of fracture(s).[134] Moreover, it bears considering that the first study in the U.S. to investigate the relationship between individual fluoride intake and bone density among children and adolescents found that total daily fluoride intake is associated with a downward trend in density in bone mineral content of the hip and whole body among the highest-exposed girls (statistically significant at $p < 0.05$, but not $p < 0.01$).[135] It also bears considering that the blood fluoride levels associated with fluoride supplement use exceed the levels that alter bone cell activity in in vitro experiments,[136] and one study has reported a reduction in alkaline phosphatase activity among children taking fluoride supplements.[137]

Fluoride supplements may thus pose a risk to skeletal health, particularly if taken for the full duration of the dosing schedule (6 months to 16 years), and if the child has suboptimal intake of calcium.[138]

e. Osteosarcoma

Fluoride's capacity to cause osteosarcoma is biologically plausible,[139] and is supported by an NTP animal study showing an increased rate of osteosarcoma among fluoride-treated *male* rats,[140] as well as epidemiological studies showing an increased rate of osteosarcoma among *young males* exposed to fluoridated water.[141] While many epidemiological studies have failed to find a relationship between fluoridated water and osteosarcoma, none of these studies has been designed in a manner that would permit them to assess the age-specific risk identified in Bassin's national case control study.[142] Bassin found that exposures to fluoridated water during the 6th to 8th year of life in boys was a significant predictor of developing osteosarcoma during adolescence, with an adjusted OR of 5.46 (95% CI 1.50 – 19.90) for exposures to fluoridated water during the 7th year of life.[143] This uncontroverted, age-specific risk of fluoride exposure has obvious potential bearing on fluoride supplementation, because under the current dosing schedule a supplemental dose of 1 mg fluoride a day is recommended for the very years that Bassin identified as the critical window of vulnerability.

2. Fluoride Supplements Lack Evidence of Effectiveness

As detailed earlier, there is a dearth of credible evidence to demonstrate the effectiveness of fluoride supplements, particularly under the current conditions of high, background exposure to topical fluorides.[144] The notable lack of such evidence has been the subject of many published reviews in the dental literature, leading to conclusions such as the following from experts in dental research and systematic reviews:

> "[Fluoride supplements] have been obediently ingested by hundreds of thousands of children since the 1960s yet the scientific basis for their use is ***very thin***."[145]
>
> "The additional reductions in dental caries to be achieved from using fluoride supplements, on top of what we already have from fluoride in drinking water, toothpaste, professional dental products, mouthrinses, and uncontrolled amounts in foods and beverages, has to be ***marginal at best***."[146]
>
> "There is thus a ***lack of evidence*** . . . to make actual good recommendations. Today, the effect of fluoride supplements in children using fluoride toothpastes on a regular basis would probably be limited."[147]

3. Fluoride Supplements Qualify as "Health Fraud Drugs"

FDA prioritizes action against what it terms "health fraud drugs." FDA defines health fraud as "[t]he deceptive promotion, advertisement, distribution or sale of articles . . . that are represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes. Such practices may be

deliberate or done without adequate knowledge or understanding of the article."

Under this definition, fluoride supplements qualify as health fraud drugs, as the manufacturers and sellers of these drugs are providing customers with demonstrably false and misleading information about the benefits of these drugs.

First, the labeling provided by both manufacturers and sellers of fluoride supplements claim that the drugs prevent cavities. Here are examples of the language that is used:

- "A dental caries preventive in pediatric populations."[148]
- "A caries prophylaxis"[149]
- "This medication is used to prevent cavities."[150]
- "This medicine is a mineral used to help prevent cavities in children."[151]
- "This supplement is used to prevent cavities."[152]
- "Makes teeth stronger and more resistant to decay."[153]

The vast majority of these companies fail to disclose that the FDA has never approved these claims.[154] The only labeling information we have found which discloses the lack of FDA approval does so in a cryptic manner (i.e., "This is not an Orange Book product") that most consumers will not understand.[155]

Second, several manufacturers include an extremely selective and misleading literature review about the benefits of fluoride supplements on their labeling. Both Libertas and Qualitest, for example, provide the results of a *single trial* conducted *in the 1960s,* without disclosing the abundant contradictory studies that have been published since.[156]

Third, we have found that the nation's four largest pharmacies (Walgreens, CVS, Rite Aid, and Walmart) routinely provide false information about the FDA-approval status of fluoride supplements when asked by prospective customers. Our volunteers visited several Walgreens, CVS, Rite Aid, and Walmart stores throughout the county, including in California, New York, North Carolina, Texas, Vermont, and Washington. The purpose of the visits was to (1) determine whether these pharmacies sold fluoride supplements, and, if so, (2) to see what information the pharmacies provide when asked about the FDA approval status of these drugs. Our volunteers presented themselves as prospective customers and audiotaped many of their conversations (recordings of which can be made available to FDA on request). As the following excerpts highlight, each of the four pharmacies consistently assured the prospective customers that fluoride supplements are FDA approved or, alternatively, that FDA approval of fluoride supplements is not necessary.

Walgreens, Austin, TX (Feb. 18, 2016)

> *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.

Walgreens, El Segundo, CA (Feb. 14, 2016)

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. . . . That's why it's back here and you can't get it [over the counter].
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.

Walgreens, Cedar Park, TX (Feb. 18, 2016)

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 [over the counter].
CUSTOMER: Everything's that's prescription at Walgreens would be FDA approved?
PHARMACIST: Yes, ma'am.
CUSTOMER: Ok, that's good to know.

CVS Pharmacy, Austin, TX (Feb. 17, 2016)

CUSTOMER: I heard that maybe it wasn't FDA-approved? That, the fluoride... Is there someone that would know that, that I could talk to?
CVS PHARMACIST ASSISTANT: Those are the pharmacists, but anything that we have as a prescription,

should be FDA approved.
CUSTOMER: Ok, and can I can confirm that with her?
CVS PHARMACIST ASSISTANT: [Goes and gets pharmacist]
CUSTOMER: Um, it's my son. He's one. And the doctor was going to prescribe some fluoride. Those are tablets, right?
CVS PHARMACIST: Yea.
CUSTOMER: And I just wanted to get some information on it before I got the prescription from him. Um, but I am worried about it because I heard that these were not FDA-approved, the fluoride. Do you know anything about that?
CVS PHARMACIST: Sodium fluoride was approved by the FDA in 1945.
CUSTOMER: And like everything here at CVS that's prescription, would be FDA-approved, correct?
CVS PHARMACIST: Yes. Prescription medication should be approved by FDA.
CUSTOMER: Ok, thank you so much for your help then. I appreciate it.
CVS PHARMACIST: You welcome.

CVS Pharmacy, Binghamton, NY (Feb. 23, 2016)

CUSTOMER: So those fluoride drops…
CVS PHARMACIST: Right.
CUSTOMER: Are they FDA approved?
CVS PHARMACIST: Of course.
CUSTOMER: And as far as you know, I can go to any CVS and get those?
CVS PHARMACIST: You have to have a prescription. But any CVS will carry it.

Rite Aid, Binghamton, NY (Feb. 23, 2016)

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.

Rite Aid, Burlington, VT (Feb. 23, 2016)

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.

Rite Aid, Chatham, NY (Feb. 23, 2016)

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 "prescription only." You need a physician's order, but it's, I mean, 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.

Walmart, Austin, TX (Feb. 18, 2016)

CUSTOMER: Ok, and for peace of mind because I'm still nervous about giving this to my son, is it FDA approved?
PHARMACIST: Yes, the prescription is controlled by the FDA. Any of the Rx items...
CUSTOMER: Are all FDA approved? So, those are FDA approved because Walmart wouldn't sell anything that was not FDA approved, would they?
PHARMACIST: Right, right. Yea, the prescription stuff all has to, under restrictions by the FDA.
CUSTOMER: Ok, so I can relax about that, that at least the FDA says it's going to be fine?
PHARMACIST: Right, right. And when we're dealing with something like the mineral fluoride, it's pretty straightforward, we're not dealing with a lot of funky chemicals. It's the fluoride ion, which is naturally occurring. They just package it into a pill.

Walmart, Hawthorne, CA (April 15, 2016)

CUSTOMER: My friend was recommended to give his kid these fluoride drops, but he was also saying that he thought that the FDA hadn't approved them. Do you know if that would be the case?
PHARMACIST: No, I hadn't heard about that.
CUSTOMER: So it is FDA approved, the fluoride drops?
PHARMACIST: Yea.
CUSTOMER: They are?
PHARMACIST: Um-hum.
CUSTOMER: Yea, because . . . if you guys are selling it as a prescription drug, it would have to be approved by the

FDA, right?
PHARMACIST: Yea, of course.
CUSTOMER: So all the fluoride drops and tablets that we would purchase by prescription here from Walmart would be FDA approved?
PHARMACIST: Yea.

As these conversations highlight, there is a staggering amount of false and deceptive information being provided about fluoride supplements by the pharmacies selling them.

FDA's definition of health fraud drugs includes drugs that are promoted with deceptive practices, whether deliberate *or* inadvertent.[157] Accordingly, whether or not the aforementioned deceptive information is being provided deliberately or inadvertently, fluoride supplements qualify as health fraud drugs.

4. Fluoride Supplements Directly Challenge FDA's OTC Monograph on Fluoride

After fifteen years of deliberation, the FDA issued an OTC Monograph for fluoride in 1995 which lays out in exacting detail the fluoride products that FDA considers to be both safe and effective for caries prevention.[158] Notably, each and every one of the products that FDA approved (i.e., toothpastes, rinses, and gels) are specifically designed to be *topically* applied to the teeth. Further, although the FDA approved a "fluoride supplement" in the monograph, FDA made it expressly clear that a fluoride supplement must be in the form of a "rinse," and *cannot be given to children under the age of 3*.[159] The sale of fluoride supplements in *drop, tablet, and lozenge* form, therefore, directly violates the framework that FDA enacted in its OTC Monograph, *especially when prescribed to children under the age of 3*.

Although the OTC Monograph on fluoride generally only applies to over-the-counter drugs, the FDA made it clear that the "fluoride supplement" defined in the monograph cannot be sold directly to consumers; it must be dispensed by health professionals.[160] Accordingly, the monograph's detailed requirements for a fluoride supplement are applicable to all fluoride supplements that are dispensed by health professionals. The FDA confirmed this in its Warning Letter to Kirkman, stating that prescription fluoride supplements "must be in accordance with 21 C.F.R. § 355.60." FDA states in the Warning Letter that "a fluoride tablet is not a dosage form permissible under [the OTC Monograph]," irrespective of whether it is sold as a prescription drug. By the same logic, prescription fluoride drops and lozenges are also barred under 21 C.F.R. § 355.60.

Manufacturers of fluoride supplements are flouting these clear requirements when they (1) use dosage forms (tablets, drops, and lozenges) that are prohibited by the monograph and (2) market these dosage forms to age groups that fall well outside the monograph's approved age range.[161] Taking enforcement actions against prescription fluoride tablets, drops, and lozenges, will therefore serve the important policy goal of "buttress[ing] the integrity" of the OTC Monograph system, and "make[] it more likely that firms will comply with . . . monograph requirements, which benefits the public health."[162]

5. Fluoride Supplements Are Violative of the FDCA in Other Ways

The FDA has stated that it prioritizes enforcement actions against unapproved new drugs that violate other provisions of the FDCA besides 21 U.S.C. § 355. This factor

again weighs strongly in favor of enforcement actions against fluoride supplements because, as FDA explained in its Warning Letter to Kirkman, the marketing of fluoride supplements that are not "rinses," and the marketing of any fluoride supplement for use among children younger than three, constitute "misbranding" violations under 21 U.S.C. § 352. All prescription fluoride supplements currently on the market are, therefore, not only unapproved new drugs, but misbranded drugs, providing yet further reason for FDA to prioritize enforcement actions against these products.

C. FDA SHOULD NOT DEFER TO PRIVATE TRADE ORGANIZATIONS

FDA should not defer enforcement action against fluoride supplements on the grounds that some private dental and medical trade organizations continue to endorse their use. Under the nation's drug laws, there is a very specific mechanism by which the safety and effectiveness of drugs are to be determined; and these determinations are to be made by the FDA,[163] not unaccountable private trade organizations—particularly where, as here, these organizations have proven resistant to responsible self-regulation.

As several dental research scholars have pointed out, the dental profession has failed to appropriately self-regulate itself on the question of fluoride supplement use. As one scholar noted, "The fact that supplements have been recommended uncritically for many years on the basis of inadequate research raises questions about the standards of dental science."[164] Other experts have observed that "[d]espite the fact that results discourage a systemic [fluoride] administration, this is still in use," thus evincing a problem of "low professional updating."[165]

Moreover, as mentioned earlier, surveys spanning three decades have demonstrated a persistent problem with inappropriate prescription practices in which fluoride supplements are prescribed—with disturbing frequency—to children living in fluoridated areas.[166] These inappropriate prescription practices have even been observed among *academic* dentists,[167] further highlighting the intransient nature of the problem.[168]

If fluoride supplements are truly safe and effective, the trade organizations that recommend them and/or the companies that manufacture them should have no problem submitting an NDA which passes muster under the governing standards of 21 U.S.C. § 355 and 21 C.F.R. § 314.126. But, until such time, the continued sale of fluoride supplements constitutes an open and notorious flouting of the legal safeguards Congress enacted to protect the American public from unsafe and ineffective drugs.

IV. ENVIRONMENTAL IMPACT

The action requested by Petitioners will not cause the release of any substance into the environment. They are categorically excluded from the requirement of environmental documentation under 21 C.F.R. § 25.30(a), 21 C.F.R. § 25.30(c), and 21 C.F.R. § 25.31.

V. ECONOMIC IMPACT

An economic impact statement will be submitted if requested by the Commissioner, per 21 C.F.R. § 10.30(b).

VI. PETITIONERS

The **Fluoride Action Network** (FAN, www.fluoridealert.org), was founded in 2000 as a project of the American Environmental Health Studies Project, Inc. FAN is an organization of scientists, doctors, dentists, environmental health researchers, and concerned citizens working to raise awareness about the impact of current fluoride exposures on human health. As part of its educational work, FAN has created a uniquely comprehensive database of published fluoride research ("Study Tracker"), which includes over 70 foreign-language studies that FAN has translated into English. These translations and FAN's research have been cited in peer-reviewed publications, including *Environmental Health Perspectives* (Choi, et al. 2012) and by national media outlets including *Scientific American*, *New York Times*, and *National Public Radio*. FAN researchers have given invited presentations before the U.S. National Research Council of the National Academies, the U.S. Environmental Protection Agency, and various governmental panels, including the Irish Forum on Fluoridation.

The **International Academy of Oral Medicine & Toxicology** (IAOMT, www.iaomt.org) has been dedicated to its mission of protecting public health through the practice of biological dentistry since it was founded in 1984. A worldwide organization of over 800 dentists, physicians, and research professionals in more than 14 countries, IAOMT's mission is accomplished by funding and promoting relevant research, accumulating and disseminating scientific information, investigating and promoting non-invasive scientifically valid therapies, and educating medical professionals, policy makers, and the general public. IAOMT members have been expert witnesses about dental products, dental practices, and oral health conditions before the U.S. Congress, the U.S. Food and Drug Administration (FDA), Health Canada, the Philippines Department of Health, the European Commission Scientific Committee on Emerging and Newly Identified Health Risks, and other government bodies around the globe. The IAOMT works to generate clinical practice guidelines, risk assessments, and other efforts relevant to regulatory and legislative activities.

VII. CERTIFICATION

The undersigned 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 the petitioners which are unfavorable to the petition.

Petitioners are represented by, and this Petition was prepared by:

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ENDNOTES

[1] The FDA's Warning Letter to Kirkman is attached hereto as **Exhibit 1**.
[2] Kirkman's response is attached as **Exhibit 2**. Because only "new drugs" require FDA approval, Kirkman contends that FDA approval for fluoride supplements is not necessary.
[3] *See, e.g.,* Letter from Melinda K. Plaisier to Hon. Ken Calvert, December 21, 2000, at p. 1, attached as **Exhibit 3**; *see also*, 21 C.F.R. § 355.1 *et seq*. (regulating fluoride as a drug when added to toothpaste, rinses, and gels as an anti-caries agent). FDA has also repeatedly, and correctly, recognized that fluoride is not an essential nutrient. *See* Compilation of FDA letters, attached as **Exhibit 4**.
[4] In its Compliance Policy Guide, FDA has correctly recognized that federal courts have construed these two exceptions "very narrowly." MARKETED UNAPPROVED DRUGS—COMPLIANCE POLICY GUIDE (Sept. 19, 2011), at 11-12 (citing cases), *available at:* fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070290.pdf. The exceptions are so narrow, in fact, that FDA has stated its belief that "it is not likely that any currently marketed prescription drug product is grandfathered or is otherwise not a new drug." *Id.* at 12.
[5] *See* Merck Index 1940, attached as **Exhibit 5**; *see also* Compilation of News Articles from 1920s/1930s discussing sodium fluoride's role as insecticide, attached as **Exhibit 6**. The rarity of using sodium fluoride as an antiseptic and antiperiodic is illustrated by the fact that the 1938 and 1940 editions of the United States Pharmacopeia do not include sodium fluoride as a substance with known therapeutic use. *See* **Exhibits 7** and **8**.
[6] *See, e.g.*, Riordan PJ. The place of fluoride supplements in caries prevention today. *Australian Dental Journal* 1996;41(5):335-42, at 335 ("Around the same time (late 1940s), fluoride supplements seem to have been marketed in the US. Fluoride supplements were being distributed regularly in US non-fluoridated areas in the early 1960s."), attached as **Exhibit 9**; Szpunar SM, Burt BA. Evaluation of appropriate use of dietary fluoride supplements in the US. *Community Dentistry & Oral Epidemiology* 1992;20(3):148-54, at 148 ("There is no firm documentation on when [fluoride supplements] first came onto the market, but it seems to have been in the mid-to-late 1940s."), attached as **Exhibit 10.**
[7] As documented below, this effectively encompasses all fluoride supplements that are currently targeted to infants, toddlers, and children. See *infra* notes 148-53 and accompanying text.
[8] *See also United States v. 225 Cartons*, 871 F.2d 409, 413 (3d Cir. 1989) ("Experts attesting to a drug's 'general recognition' of efficacy must base their opinions on evidence that meets the FDA's extensive regulations governing whether a study is 'adequate and well-controlled' for purposes of the FDC Act.")
[9] *Premo Pharm*, 629 F.2d at 802.
[10] COMPLIANCE POLICY GUIDE, *supra* note 4, at 12 (emphases added).
[11] Tubert-Jeannin S, et al. (2011). Fluoride supplements (tablets, drops, lozenges or chewing gums) for preventing dental caries in children. The Cochrane Library. p. 25, attached as **Exhibit 11.**
[12] *Id.*
[13] Grandjean P, Landrigan PJ. Neurobehavioral effects of developmental toxicity. *Lancet Neurology* 2014;13(3):330-38, attached as **Exhibit 12.**
[14] National Research Council (NRC). (2006). Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, Washington D.C. at pp.224-267, attached as **Exhibit 13.**
[15] *See, e.g.*, NRC, *supra* note 14, at 165 ("The weight of evidence supports the conclusion that lifetime exposure to fluoride at drinking water concentrations of 4 mg/L and higher is likely to increase fracture rates in the population, compared with exposure to fluoride at 1 mg/L, particularly in some susceptible demographic groups that are prone to accumulating fluoride into their bones."); Turner CH. Fluoride and the FDA: a curious case. (letter) *Journal of Bone and Mineral Research* 1996;11(9):1369-71 ("[O]ne cannot help but be alarmed by the negative effects of fluoride on bone strength consistently demonstrated in animal models."), attached as **Exhibit**

14; Sogaard CH, et al. Effects of fluoride on rat vertebral body biomechanical competence and bone mass. *Bone* 1995;16:163-9 ("[A]n overwhelming majority of the [animal] investigations mentioned found no effect or a negative effect of fluoride on bone strength…"), attached as **Exhibit 15**.

[16] NRC, *supra* note 14, at 275 ("Osteosarcoma presents the greatest a priori plausibility as a potential cancer target site because of fluoride's deposition in bone, the NTP animal study findings of borderline increased osteosarcomas in male rats, and the known mitogenic effect of fluoride on bone cells in culture. Principles of cell biology indicate that stimuli for rapid cell division increase the risks for some of the dividing cells to become malignant, either by inducing random transforming events or by unmasking malignant cells that previously were in nondividing states."); Mihashi M, Tsutsui T. Clastogenic activity of sodium fluoride to rat vertebral body-derived cells in culture. *Mutation Research* 1996;368:7-13 ("Because the origin of osteosarcoma is considered to be osteoblastic/osteogenic cells, the ability of sodium fluoride to induce chromosome aberrations in these cells provides a mechanistic basis for the occurrence of osteosarcomas observed in sodium fluoride treated animals in the NTP study. Ingested fluoride is accumulated in bone, suggesting that osteoblastic/osteogenic cells in the bone microenvironment can be exposed to high levels of fluoride during bone formation. Our data and the NTP findings provide evidence that bone can be an organ for NaF carcinogenesis."), attached as **Exhibit 16**; Freni S.C., Gaylor, D.W. International trends in the incidence of bone cancer are not related to drinking water fluoridation. *Cancer* 1992;70: 611-8 ("[T]he carcinogenicity of fluoride is consistent with growth stimulation of osteoblasts, unscheduled DNA synthesis by human fibroblasts, and transformation of embryonal hamster fibroblasts into transplantable sarcoma cells. Osteoblasts are differentiated fibroblasts, and fluoride is accumulated in the skeleton. Therefore, osteosarcoma would be the natural target effect to look for in a cancer bioassay of fluoride, and an excess of osteosarcoma in rats exposed to fluoride in drinking water clearly confirms an a priori hypothesis."), attached as **Exhibit 17**.

[17] For a discussion of this evidence, see *infra* notes 88-143 and accompanying text.

[18] Ismail AI, Hasson H. Fluoride supplements, dental caries and fluorosis: a systematic review. *Journal of the American Dental Association* 2008;139(11):1457-68, at 1457 (""Mild-to-moderate dental fluorosis is a significant side effect."), attached as **Exhibit 18**; Ismail AI, Bandekar RR. Fluoride supplements and fluorosis: a meta-analysis. *Community Dentistry & Oral Epidemiology* 1999;27(1):48-56 ("[F]luoride supplements during the first 6 years of life is associated with a significant increase in the risk of developing dental fluorosis."), attached as **Exhibit 19.**

[19] Riordan PJ. Fluoride supplements for young children: an analysis of the literature focusing on benefits and risks. *Community Dentistry & Oral Epidemiology* 1999;27(1):72-83, at 81, attached as **Exhibit 20**.

[20] *See, e.g.*, Suzuki M, Bartlett JD. Sirtuin1 and autophagy protect cells from fluoride-induced cell stress. *Biochimica et biophysica acta* 2014;1842(2):245-55, attached as **Exhibit 21**; Sierant ML, Bartlett JD. Stress response pathways in ameloblasts: implications for amelogenesis and dental fluorosis. *Cells* 2012;1(3):631-45, attached as **Exhibit 22**; Bronckers AL, et al. The impact of fluoride on ameloblasts and the mechanisms of enamel fluorosis. *Journal of Dental Research* 2009;88(10):877-93, attached as **Exhibit 23**.

[21] Although not definitive, some research has reported associations between mild and/or moderate fluorosis (TF Score $\geq$ 2/ to $\leq$ 4) and reduced IQ, bone fracture, and caries. *See, e.g.*, Das K, Mondal NK. Dental fluorosis and urinary fluoride concentration as a reflection of fluoride exposure and its impact on IQ level and BMI of children of Laxmisagar, Simlapal Block of Bankura District, W.B., India. *Environmental Monitoring & Assessment* 2016;188(4):218, attached as **Exhibit 24**; Alarcon-Herrera MT, et al. Well water fluoride, dental fluorosis, bone fractures in the Guadiana Valley of Mexico. *Fluoride* 2001;34(2):139-49, attached as **Exhibit 25**; Cortes DF, et al. Drinking water fluoride levels, dental fluorosis, and caries experience in Brazil. *Journal of Public Health Dentistry* 1996;56:226-8, attached as **Exhibit 26**.

[22] Luke J. (1997). The Effect of Fluoride on the Physiology of the Pineal Gland. Ph.D. Thesis. University of Surrey, Guildford. at 176 ("The safety of the use of fluorides ultimately rests on the assumption that the developing enamel organ is most sensitive to the toxic effects of fluoride. The

results from this study suggest that-the pinealocytes may be as susceptible to fluoride as the developing enamel organ."), attached as **Exhibit 27.**

[23] Spittle B. Allergy and hypersensitivity to fluoride. *Fluoride* 1993;26:267-73, attached as **Exhibit 28**; Ferguson DB, Stephen KW. Plasma alkaline phosphatase levels in subjects taking fluoride tablets. *Caries Research* 1980;14(4):233-4, attached as **Exhibit 29**; Zanfanga PE. Allergy to fluoride. *Fluoride* 1976;9: 36-41, attached as **Exhibit 30**; Shea JJ, et al. Allergy to fluoride. *Annals of Allergy* 1967;25:388-91, attached as **Exhibit 31**; Feltman R. Prenatal and postnatal ingestion of fluoride salts: A progress report. *Dental Digest* 1956;62:353-357, attached as **Exhibit 32**. Hypersensitivity to fluoride has also been observed from use of topical fluoride products, including toothpaste. *See, e.g.*, Camarasa JG, et al. Contact urticaria from sodium fluoride. *Contact Dermatitis* 1993; 28:294, attached as **Exhibit 33**; Mellette JR, et al. Perioral dermatitis. *Journal of the Association of Military Dermatologists* 1983;9: 3-8, attached as **Exhibit 34**; Mellette JR, et al. Fluoride tooth paste: A cause of perioral dermatitis. *Archives of Dermatology* 1976;112: 730-731, attached as **Exhibit 35**.

The existence of hypersensitivity to fluoride toothpaste is, in fact, well recognized by dermatologists. *See, e.g.*, Brun R. Recurrent Benign Aphthous Stomatitis and Fluoride Allergy. *Dermatology* 2004;208:181, attached as **Exhibit 36**; Fuchs SS. Fluoride and dermatitis. *Journal of the American Dental Association* 2003;134: 1167, attached as **Exhibit 37**.

[24] Griffin SO, et al. Esthetically objectionable fluorosis attributable to water fluoridation. *Community Dentistry & Oral Epidemiology* 2002;30:199-209, attached as **Exhibit 38**.

[25] *See, e.g.*, Tellez M, et al. Dental fluorosis, dental caries, and quality of life factors among schoolchildren in a Colombian fluorotic area. *Community Dental Health* 2012;29(1):95-99, attached as **Exhibit 39**; Marshman Z, et al. The impact of developmental defects of enamel on young people in the UK. *Community Dentistry & Oral Epidemiology* 2008;37:45-57, attached as **Exhibit 40**; Levy SM, et al. Factors associated with parents' esthetic perceptions of children's mixed dentition fluorosis and demarcated opacities. *Pediatric Dentistry* 2005;27(6):486-92, attached as **Exhibit 41**; Alkhatib MN, et al. Aesthetically objectionable fluorosis in the United Kingdom. *British Dental Journal* 2004;197:325-28, attached as **Exhibit 42**; McKnight CB, et al. A pilot study of dental students' esthetic perceptions of computer-generated mild dental fluorosis compared to other conditions. *Journal of Public Health Dentistry* 1999;59(1):18-23, attached as **Exhibit 43**; Lalumandier JA, Rozier RG. Parents' satisfaction with children's tooth color: fluorosis as a contributing factor. *Journal of the American Dental Association* 1998;129:1000-6*, attached as* **Exhibit 44**; Riordan PJ. Perceptions of dental fluorosis. *Journal of Dental Research* 1993;72:1268-74, attached as **Exhibit 45**.

[26] *See, e.g.*, Tellez, *supra* note 25; Marshman, *supra* note 25; Riordan, *supra* note 25.

[27] *See, e.g.*, Harter S. Is self-esteem only skin deep? The inextricable link between physical appearance and self-esteem. *Reclaiming Children and Youth* 2000;9(3):133-38, attached as **Exhibit 46**.

[28] The National Institute of Mental Health's conclusion is quoted on page IX-14 of EPA's October 21, 1985 Drinking Water Criteria Document on Fluoride, which is attached as **Exhibit 47**.

[29] *See, e.g.*, Burt BA. The case for eliminating the use of dietary fluoride supplements for young children. *Journal of Public Health Dentistry* 1999;59(4):269-74, at 272 (""When supplements were first introduced, it was assumed that fluoride's cariostatic effects were largely preeruptive."), attached as **Exhibit 48**; Szpunar, *supra* note 6, at 148 ("In the early days of fluoride research, scientific consensus was that the primary action of fluoride was pre-eruptive. Because dental fluorosis was systemic in origin, it was assumed that the associated favorable effect, caries inhibition, was also of systemic origin. . . . Given such faith in pre-eruptive fluoride action, it made sense to prescribe fluoride supplements for children who did not consume optimally fluoridated water.").

[30] Featherstone, JDB. The science and practice of caries prevention. *Journal of the American Dental Association* 2000;131:887-99, at 891, attached as **Exhibit 49**.

[31] Centers for Disease Control and Prevention. Recommendations for Using Fluoride to Prevent and Control Dental Caries in the United States. *Morbidity and Mortality Weekly Report* 2001;50(RR14): 1-42, at 4, attached as **Exhibit 50.**

[32] NRC, *supra* note 14, at 13.

[33] Fejerskov O. Changing paradigms in concepts on dental caries: consequences for oral health care. *Caries Research* 2004;38:182-91, attached as **Exhibit 51**.
[34] Burt, *supra* note 29, at 272.
[35] Tubert-Jeannin, *supra* note 11, at 29.
[36] Ismail & Hasson, *supra* note 18, 1467 ("Like most recent dental or medical systematic reviews, our review also demonstrated that the majority of the studies were highly biased.").
[37] *Id.* at 1464 ("[T]he majority of [the supplement/caries] studies were conducted at a time when fluoridated dentrifices were not used widely.")
[38] *E.g.*, Tomasin L, et al. The role of fluoride tablets in the prophylaxis of dental caries. A literature review. *Annali di Stomatologia* 2015;VI(1):1-5, attached as **Exhibit 52**; Tubert-Jeannin, *supra* note 11; Burt, *supra* note 29; Riordan, *supra* note 6, at 340.
[39] Stecksen-Blicks C, et al. Effect of xylitol and xylitol-fluoride lozenges on approximal caries development in high caries-risk children. *International Journal of Paediatric Dentistry* 2008;18:170-77, attached as **Exhibit 53**; Kallestal C. The effect of five years' implementation of caries-preventive methods in Swedish high-risk adolescents. *Caries Research* 2005;39:20-26, attached as **Exhibit 54**; Wang NJ, Riordan PJ. Fluoride supplements and caries in a non-fluoridated population. *Community Dentistry & Oral Epidemiology* 1999;27:117-23, attached as **Exhibit 55**; Kalsbeek H, et al. Use of fluoride tablets and effect on prevalence of dental caries and dental fluorosis. *Community Dentistry & Oral Epidemiology* 1992;20:241-45, attached as **Exhibit 56**; Stephen KW, et al. Combined fluoride therapies: a 6-year double-blind school-based preventive dentistry study in Inverness, Scotland. *Community Dentistry & Oral Epidemiology* 1990;18:244-48, attached as **Exhibit 57**.
[40] Riordan, *supra* note 6, at 340.
[41] Tubert-Jeannin, *supra* note 11, at 2.
[42] Limeback H. Introduction to conference. *Community Dentistry & Oral Epidemiology* 1999;27:27-30, at 29 ("The effectiveness of these products in preventing dental caries is low in school-aged children . . . and not well evaluated in infants and toddlers . . . .") , attached as **Exhibit 58**.
[43] Ismail & Hasson, *supra* note 18, at 1464.
[44] *Id.* at 1463-64 ("During the first three years of life, however, there is only limited evidence regarding the effectiveness of fluoride supplements in preventing caries . . . . Regarding children aged 3 years to younger than 6 years, there is inconsistent and weak evidence regarding the effectiveness of supplements on primary teeth and permanent teeth.").
[45] Rozier RG, et al. Evidence-based clinical recommendations on the prescription of dietary fluoride supplements for caries prevention. *Journal of the American Dental Association* 2010;141(12):1480-89, attached as **Exhibit 59**.
[46] Tubert-Jeannin, *supra* note 11, at 29 ("Many countries or international institutions recommend the use of fluoride supplements for children who are at high caries risk. The effect of the different supplementation regimens proposed (doses, age at start, level of risk, modalities of administration) is unknown and would need evaluation."). In fact, some recent studies have failed to find any benefit of supplements in high-caries risk populations. Stecksen-Becks, *supra* note 39; Kallestal, *supra* note 39.
[47] Stecksen-Becks, *supra* note 39; Kallestal, *supra* note 39.
[48] Ismail & Hasson, *supra* note 18, at 1467.
[49] Riordan, *supra* note 19, at 72.
[50] *Id.* at 79.
[51] Ismail, *supra* note 18, at 165.
[52] Tubert-Jeannin, *supra* note 11, at 28
[53] Tomasin, *supra* note 38, at 1.
[54] Burt, *supra* note 29, at 272
[55] Riordan, *supra* note 6, at 340.
[56] Tubert-Jeannin, *supra* note 11, at 2.
[57] Moyers MA. Prevention of dental caries in children from birth through age 5 years: US Preventive Services Task Force recommendation statement. *Pediatrics* 2014;133(6):1102-11, attached as **Exhibit 60**; Rozier, *supra* note 45 ("The panel concluded that dietary fluoride

supplements should be prescribed only for children who are at high risk of developing caries and whose primary source of drinking water is deficient in fluoride.").

[58] Burt, *supra* note 29.

[59] Narendran SN, et al. Fluoride knowledge and prescription practices among dentists. *Journal of Dental Education* 2006;70(9): 956-64, 957, attached as **Exhibit 61**.

[60] These experts have reached this conclusion despite only considering one of the potential risks of fluoride exposure (i.e., dental fluorosis). If the other potential risks are considered (e.g., neurotoxicity and endocrine disruption), the risk/benefit argument for not using supplements becomes even more glaringly obvious.

[61] Burt, *supra* note 29, at 271-72.

[62] Tomasin, *supra* note 38, at 4.

[63] Szpunar, *supra* note 6, at 152.

[64] Tubert-Jeannin, *supra* note 11, at 28.

[65] Warren J, et al. Considerations on optimal fluoride intake using dental fluorosis and dental caries outcomes: A longitudinal study. *Journal of Public Health Dentistry* 2009;69:111-15, at 114-15, attached as **Exhibit 62**.

[66] As examples, we have attached the labeling information used by Libertas Pharma, Inc. (**Exhibit 63**), PureTek (**Exhibit 64**), Qualitest (**Exhibit 65**), and Sancilio & Company (**Exhibit 66**), which we obtained form the National Library of Medicine's (NLM) "DailyMed" online database. Please note that the "disclaimer" provided at the top of the first page for each of these labeling documents (i.e., "This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA.") is from the NLM; it is *not* included in the labelling provided with the actual drugs.

[67] Whitford GM. The physiological and toxicological characteristics of fluoride. *Journal of Dental Research* 1990;69(Spec Issue):539-49, at 543-44 ("The fact that the schedule is based on relatively wide age intervals leads to substantial variations in the dosages when adjusted for body weight. . . . It appears that the currently recommended supplementation schedule should be refined for the purpose of narrowing the range of doses adjusted for body weight."), attached as **Exhibit 67**; *see also* Szpunar, *supra* note 6, at 152 ("[B]ody weight, altitude, and health status may need to be factored into the prescription schedule.").

[68] Riordan (1996), *supra* note 6, at 339.

[69] As examples, please see the labeling information used by PureTek and Sancilio, *supra* note 66.

[70] Levy SM, Guha-Chowdhury N. (1999). Total fluoride intake and implications for dietary fluoride supplementation. *Journal of Public Health Dentistry* 59: 211-23, at 216-17, attached as **Exhibit 68**. *See also* Ekstrand J, et al. Plasma fluoride concentrations in pre-school children after ingestion of fluoride tablets and toothpaste. *Caries Research* 1983;17:379-84 (demonstrating that ingestion of toothpaste can cause comparable increases in blood fluoride levels as ingestion of 0.5 mg fluoride tablets), attached as **Exhibit 69**.

[71] Levy & Guha-Chowdhury, *supra* note 70, at 219.

[72] Kiritsy MC, et al. Assessing fluoride concentrations of juices and juice-flavored drinks. *Journal of the American Dental Association* 1996;127(7):895-902, at 901, attached as **Exhibit 70**.

[73] Ismail AI. Fluoride supplements: current effectiveness, side effects, and recommendations. *Community Dentistry & Oral Epidemiology* 1994;22(3):164-72, at 169, attached as **Exhibit 71.**

[74] American Academy of Pediatric Website, attached as **Exhibit 72.**

[75] See, for example, the labeling materials for Puretek & Sancilio, *supra* note 66.

[76] See, for example, the labeling materials for Libertas & Qualitest, *supra* note 66.

[77] COMPLIANCE POLICY GUIDE, *supra* note 4, at 9-10.

[78] FDA approved Enziflur as safe in 1945, at a time when it was a calcium fluoride-based formulation. *See* PHYSICIAN'S DESK REFERENCE (1947), at 270, attached as **Exhibit 73**; Council on Dental Therapeutics. Preliminary comments on dental products. *Journal of the American Dental Association* 1948;37:588-89, at 589, attached as **Exhibit 74.** At some point prior to the 1960s, Enziflur was reformulated to use sodium fluoride instead of calcium fluoride. *See* FDA's Enziflur DESI Case File, attached as **Exhibit 75**.

[79] *See* Enziflur DESI Case File, *supra* note 78.

[80] Sodium Fluoride, Ascorbic Acid, and Ergocalciferol Lozenge; Notice of Opportunity for Hearing on Proposal to Withdraw Approval of New Drug Application, 37 Fed. Reg. 24203 (Nov. 15, 1972), attached as **Exhibit 76**; "NDA Withdrawn for Fluoride and Vitamin Combinations," DRUG THERAPY (June 1975), attached as **Exhibit 77.**

[81] *See* Enziflur DESI Case File, *supra* note 78, at 2 & 6.

[82] *See id*. at 2 (identifying the "Documentation" upon which NRC based its revised ruling); *id*. at 3 (listing the publications on Enziflur that NRC considered as part of its review).

[83] *See id*. at 6.

[84] The Enziflur DESI case file shows that NRC treated the effectiveness and need for fluoride supplements as an assumption. *See id*. at 6 ("*Even if there is a need for dietary fluoride supplementation*, combining the fluoride with vitamins is contraindicated because of the inflexibility already mentioned and because the cost to the consumer may be raised considerably." (emphasis added)). Accordingly, to interpret the NRC's DESI review of Enziflur as demonstrating the effectiveness of fluoride supplements would run afoul of Congress's statutory mandate that the effectiveness of drugs be based on "substantial evidence." *See Weinberger v. Hynson, Westcott & Dunning, Inc*., 412 U.S. 609, 629-30 (1973); *Weinberger v. Bentex Pharms., Inc*., 412 U.S. 645, 653 (1973). *See also Weinberger*, 412 U.S. at 619 ("The hearings underlying the 1962 Act show a marked concern that impressions or beliefs of physicians, no matter how fervently held, are treacherous.").

[85] COMPLIANCE POLICY GUIDE, *supra* note 4, at 4-5.

[86] See *supra* notes 18-19 and accompanying text.

[87] See *supra* note 23 and accompanying text.

[88] *See, e.g.*, Narendran, *supra* note 59; Pendrys DG. Risk of enamel fluorosis in nonfluoridated and optimally fluoridated populations. *Journal of the American Dental Association* 2000;131:746-55, *attached as* **Exhibit 78***;* Roberts MW, et al. Fluoride supplement prescribing and dental referral patterns among academic pediatricians. *Pediatrics* 1998;101(1):e6, attached as **Exhibit 79**; Pendrys DG. Risk of fluorosis in a fluoridated population. *Journal of the American Dental Association* 1995;126:1617-24, attached as **Exhibit 80**; Jones KF, Berg JH. Fluoride supplementation: a survey of pediatricians and pediatric dentists. *American Journal of Diseases of Children* 1992;146:1488-91, attached as **Exhibit 81**; Kuthy RA, McTigue DJ. Fluoride prescription practices of Ohio physicians. *Journal of Public Health Dentistry* 1987;47(4):172-76, attached as **Exhibit 82**; Levy SM, Rozier RG. Use of systemic fluoride supplements by North Carolina dentists. *Journal of the American Dental Association* 1987;114:347-50, attached as **Exhibit 83**; Siegel C, Gutgesell ME. Fluoride supplementation in Harris County, Texas. *American Journal of Diseases of Children* 1982;136:61-63, attached as **Exhibit 84**; Margolis FJ, et al. Fluoride supplements for children. A survey of physicians' prescription practices. *American Journal of Diseases of Children* 1980;134:865-68, attached as **Exhibit 85**.

[89] In one recent survey, 57.4% of responding dentists stated that they did not consider a child's use of fluoride toothpaste when determining whether to prescribe fluoride supplements. Narendran, *supra* note 59, at 960 Tbl.3.

[90] Pendrys (1995), *supra* note 88, at 1618.

[91] The following studies demonstrate that the fluoride levels in processed beverages and foods can contribute significantly to a child's daily intake of fluoride: Fein NJ, Cerklewski FL. Fluoride content of foods made with mechanically separated chicken. *Journal of Agricultural Food Chemistry* 2001; 49(9):4284-6, attached as **Exhibit 86**; Heilman JR, et al. Fluoride concentrations of infant foods. *Journal of the American Dental Association* 1997;128(7):857-63, attached as **Exhibit 87**; Kiritsy, *supra* note 72; Stannard JG, et al. Fluoride levels and fluoride contamination of fruit juices. *Journal of Clinical Pediatric Dentistry* 1991;16(1):38-40, attached as **Exhibit 88**.

[92] The wide variability in how humans respond to fluoride is supported by many lines of evidence. We discuss here two of these lines of evidence. First, there is evidence showing that a small percentage of humans experience hypersensitive reactions, including skin rashes, gastric distress, and headaches, at the dose range used in fluoride prophylactic programs for caries prevention, including both systemic and topical fluorides. See *supra* note 23 for several of the studies documenting this. Second, studies on the bone response to fluoride in humans—including clinical trials where fluoride has been used as an experimental osteoporosis treatment,

epidemiological studies of endemic water-borne fluorosis, and occupational studies of industrial fluorosis—have consistently shown huge variations in the doses that cause detectable bone changes, the form these changes take, and the symptoms associated with them. *See, e.g.*, Chachra D, et al. The long-term effects of water fluoridation on the human skeleton. *Journal of Dental Research* 2010 89:1219-1223 ("Fluoride incorporation into bone depends on many factors, including ingestion from sources in addition to water, age, duration of residency, renal function and other disease states, remodeling rate, and genetic susceptibility. About 40% of the population in areas with water supplies naturally fluoridated at very high levels are unaffected by skeletal fluorosis, and about a third of patients who receive fluoride as a therapy for osteoporosis are described as 'nonresponders,' indicating that intrinsic susceptibility to fluoride varies with the individual. A genetic basis for these differences is supported by research with different strains of mice. In a large, diverse urban center like Toronto, therefore, one would expect that the population would display a range of genetic susceptibilities to fluoride…"), attached as **Exhibit 89**; Wang Y, et al. Endemic fluorosis of the skeleton: radiographic features in 127 patients. *American Journal of Roentgenology* 1994;162: 93-8 ("It has been a consistent observation in epidemiologic studies that the clinical severity of fluoride-induced toxic effects is highly variable among persons living in the same environment and exposed to the same risk of fluoride ingestion."), attached as **Exhibit 90**; Boivin G, et al. Relationship between bone fluoride content and histological evidence of calcification defects in osteoporotic women treated long term with sodium fluoride. *Osteoporosis International* 1993;3:204-208 ("The bioavailability [of fluoride] may be markedly different from one patient to another."), attached as **Exhibit 91**; Dure-Smith BA, et al. (1991). Fluoride therapy for osteoporosis: A review of dose response, duration of treatment, and skeletal sites of action. *Calcified Tissue International* 49(Suppl): S64-S67 ("The osteogenic response (to fluroide) shows marked interpatient variation."), attached as **Exhibit 92**; Runge H, Franke J. Radiological modifications of the skeletal system among aluminum smelter workers: A 15 year retrospective study. *Fluoride* 1989;22:157-164 ("Individual differences in sensitivity to noxious fluoride seems to be important… [I]t is quite possible to be an aluminum smelter worker for 30 years or longer without showing fluoride-caused bone changes, whereas others develop symptoms of fluorosis after only 10 years…"), attached as **Exhibit 93**; Anand JK, Roberts JT. Chronic fluorine poisoning in man: a review of literature in English (1946-1989) and indications for research. *Biomedicine & Pharmacotherapy* 1990;44: 417-420 ("We suggest that predisposition to fluorosis (chronic toxicity) is biochemically mediated and genetically determined. This would explain the marked variation in fluorosis prevalence in areas with comparable levels of fluoride intake and the selectivity of the disease within the same area. Further studies are necessary to elucidate the complex interaction between calcium, iodine, sex hormones, vitamins and fluoride ions."), attached as **Exhibit 94**; Christie DP. The spectrum of radiographic bone changes in children with fluorosis. *Radiology* 1980;136:85-90 ("The considerable individual variability of skeletal response to excessive fluoride ingestion implies that causative factors other than total daily ingestion of fluoride exist."), attached as **Exhibit 95**.

[93] *See, e.g.*, Irigoyen-Camacho ME et al. Nutritional status and dental fluorosis among schoolchildren in communities with different drinking water fluoride concentrations in a central region in Mexico. *Science of the Total Environment* 2016;541:512-19, attached as **Exhibit 96**; Simon MJ, et al. High fluoride and low calcium levels in drinking water is associated with low bone mass, reduced bone quality and fragility fractures in sheep. *Osteoporosis International* 2014;25(7):1891-1903, attached as **Exhibit 97**; Teotia M, et al. Endemic chronic fluoride toxicity and dietary calcium deficiency interaction syndromes of metabolic bone disease and deformities in India: year 2000. *Indian Journal of Pediatrics* 1998;65:371-81, attached as **Exhibit 98**; Lin FF, et al. The relationship of a low-iodine and high-fluoride environment to subclinical cretinism in Xinjiang. *Iodine Deficiency Disorder Newsletter*. 1991;7(3):24-25, attached as **Exhibit 99**; Guan ZZ, et al. Synergistic action of iodine-deficiency and fluorine-intoxication on rat thyroid. *Chinese Medical Journal* 1988;101(9):679-84, attached as **Exhibit 100**; Massler M, Schour I. Relation of endemic dental fluorosis to malnutrition. *Journal of the American Dental Association* 1952;44: 156-65, attached as **Exhibit 101**.

[94] *See, e.g.*, Zhang S, et al. Modifying effect of COMT gene polymorphism and a predictive role for proteomics analysis in children's intelligence in endemic fluorosis area in Tianjin, China.

Toxicological Sciences 2015;144(2):238-45, attached as **Exhibit 102**; Kobayashi CA, et al. Bone response to fluoride exposure is influenced by genetics. *PLoS One* 2014;9(12):e11343, attached as **Exhibit 103**; Carvalho JG, et al. Influence of genetic background on fluoride metabolism in mice. *Journal of Dental Research* 2009;88(11):1054-58, attached as **Exhibit 104;** Mousny M, et al. The genetic influence on bone susceptibility to fluoride. *Bone* 2006;39(6):1283-9, attached as **Exhibit 105**.

[95] Schiffl H. Fluoridation of drinking water and chronic kidney disease: absence of evidence is not evidence of absence. *Nephrology Dialysis Transplantation* 2008;23:411, attached as **Exhibit 106**; Lyaruu DM, et al. The effect of fluoride on enamel and dentin formation in the uremic rat incisor. Pedi*atric Nephology* 2008;23:1973-79, attached as **Exhibit 107**; Ibarra-Santana C, et al. Enamel hypoplasia in children with renal disease in a fluoridated area. *Journal of Pediatric Dentistry* 2007;31(4):274-8, attached as **Exhibit 108**; Johnson W, et al. Fluoridation and bone disease in renal patients. In: E Johansen, DR Taves, TO Olsen, Eds. Continuing Evaluation of the Use of Fluorides. AAAS Selected Symposium. Westview Press, Boulder, Colorado (1979), at 275-293, attached as **Exhibit 109**; Greenberg LW, et al. Nephrogenic diabetes insipidus with fluorosis. *Pediatrics* 1974;54(3):320-2, attached as **Exhibit 110**; Juncos LI, Donadio JV. Renal failure and fluorosis. *Journal of the American Medical Association* 1972;222:783-5, attached as **Exhibit 111**.

[96] This includes both diabetes mellitus and diabetes insipidus. *See, e.g.*, Seow WK, Thomsett MJ. Dental fluorosis as a complication of hereditary diabetes insipidus: studies of six affected patients. *Pediatric Dentistry* 1994;16(2):128-32, attached as **Exhibit 112**; Klein H. Dental fluorosis associated with hereditary diabetes insipidus. *Oral Surg Oral Med Oral Pathol.* 1975;40(6):736-41, attached as **Exhibit 113**; Hanhijarvi H. Inorganic plasma fluoride concentrations and its renal excretion in certain physiological and pathological conditions in man. Fluoride 1975;8(4):198-207, attached as **Exhibit 114**; Greenberg, *supra* note 95.

[97] Leite GA, et al. Exposure to lead exacerbates dental fluorosis. *Archives of Oral Biology* 2011;56(7):695-702, attached as **Exhibit 115**; Niu R, et al. Decreased learning ability and low hippocampus glutamate in offspring rats exposed to fluoride and lead. *Environmental Toxicology & Pharmacology* 2009;28(2):254-8, attached as **Exhibit 116**; Mahaffey KR, Stone CL. Effect of high fluorine (F) intake on tissue lead (Pb) concentrations. *Federation Proceedings* 1976;35:256, attached as **Exhibit 117**.

[98] *See, e.g.*, Burt BA, et al. Dietary patterns related to caries in a low-income adult population. *Caries Research* 2006;40:473-80, attached as **Exhibit 118**; Adelaja AO, et al. Income and racial differentials in selected nutrient intakes. *American Journal of Agricultural Economics* 1997; 79(5):1452-60, attached as **Exhibit 119**; *see also* Watters JL, et al. Associations of antioxidant nutrients and oxidative DNA damage in healthy African-American and White adults. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(7):1428-36, attached as **Exhibit 120**.

[99] *E.g.* , Brown MJ, Margolis S. Lead in drinking water and human blood lead levels in the United States. *Morbidity and Mortality Weekly Report* 2012;61(4):1-9, attached as **Exhibit 121**.

[100] Rozier, *supra* note 45, at 1480.

[101] *See, e.g.*, Dye BA, et al. Trends in paediatric dental caries by poverty status in the United States 1988-1994 and 1999-2004. *International Journal of Paediatric* Dentistry 2010;20:132-43, attached as **Exhibit 122**.

[102] Beltrán-Aguilar ED, et al. Prevalence and Severity of Dental Fluorosis in the United States, 1999–2004. Centers for Disease Control. 2010 Nov.; NCHS Data Brief No. 53, Fig.3, attached as **Exhibit 123**.

[103] In the 1940s and 1950s, it was estimated that less than 10% of children in *fluoridated* areas develop fluorosis, and only in its mildest forms. *See* National Research Council. Report of the Ad Hoc Committee on the Fluoridation of Water Supplies. Nov. 29, 1951, at 2 ("At approximately 1.0 ppm less than 10 percent of children show the least detectable evidence of disturbances in enamel formation, which are not visible except to the trained eye of the examining dentist.") , attached as **Exhibit 124.**

[104] The fluorosis data from the 2011-12 NHANES Survey is available in raw form at: http://wwwn.cdc.gov/nchs/nhanes/search/DataPage.aspx?Component=Examination&CycleBeginYear=2011. To allow direct comparison with the 1999-20014 NHANES Survey, Petitioners have

calculated the fluorosis rates for all age groups (6 to 19 years), as well as the fluorosis rates for the 6-11, 12-15, and 16-19 age groups. This data is attached as **Exhibit 125**.

[105] Grandjean & Landrigan, *supra* note 13, at 334 Table 2. The total number is 12 if ethanol is included.

[106] For a small sampling of these studies, *see*: Choi A, et al. Developmental fluoride neurotoxicity: a systematic review and meta-analysis. *Environmental Health Perspectives* 2012; 120(10):1362-8, attached as **Exhibit 126**; Zhang, *supra* note 94; Rocha-Amador D, et al. Decreased intelligence in children and exposure to fluoride and arsenic in drinking water. *Cadernos de Saude Publica* 2007;23(Suppl 4):S579-87, attached as **Exhibit 127**; Wang SX, et al. Arsenic and fluoride exposure in drinking water: children's IQ and growth in Shanyin county, Shanxi province, China. *Environmental Health Perspectives* 2007;115(4):643-7, attached as **Exhibit 128**; Xiang Q, et al. Effect of fluoride in drinking water on children's intelligence. *Fluoride* 2003;36:84-94 & 198-99, attached as **Exhibit 129**; Dong YT, et al. Deficit in learning and memory of rats with chronic fluorosis correlates with the decreased expressions of M1 and M3 muscarinic acetylcholine receptors. *Archives of Toxicology* 2015;89(11):1981-91, attached as **Exhibit 130**; Niu, *supra* note 97.

[107] For a small sampling of these studies, *see*: Choi A, et al. Association of lifetime exposure to fluoride and cognitive functions in Chinese children: A pilot study. *Neurotoxicology & Teratology* 2015;47:96-101, attached as **Exhibit 131**; Rocha-Amador, D. et al Use of the Rey-Osterrieth complex figure test for neurotoxicity evaluation of mixtures in children. *Neurotoxicology* 2009;30(6):1149-54, attached as **Exhibit 132**; Han H, et al. Effects of chronic fluoride exposure on object recognition memory and mRNA expression of SNARE complex in hippocampus of male mice. *Biological Trace Element Research* 2014;158(1):58-64, attached as **Exhibit 133**.

[108] Li J, Yao L, Shao Q-L. Effects of high-fluoride on neonatal neurobehavioural development. *Chinese Journal of Endemiology* 2004;23:464-465. (Republished in *Fluoride* 2008;41:165-70), attached as **Exhibit 134**; Guo Z, et al. Study on neurobehavioral function of workers occupationally exposed to fluoride. *Industrial Health and Occupational Disease* 2001;27:346-348. (Republished in *Fluoride* 2008; 41:152-55), attached as **Exhibit 135**; Ekambaram P, Paul V. Calcium preventing locomotor behavioral and dental toxicities of fluoride by decreasing serum fluoride level in rats. *Environmental Toxicology and Pharmacology* 2001;9(4):141-146, attached as **Exhibit 136**; Mullenix P, et al. (1995). Neurotoxicity of sodium fluoride in rats. *Neurotoxicology and Teratology* 1995;17:169-177, attached as **Exhibit 137**. *See also* Malin AJ, Till C. Exposure to fluoridated water and attention deficit hyperactivity disorder prevalence among children and adolescents in the United States: an ecological association. *Environmental Health* 2015;14:17, attached as **Exhibit 138**.

[109] Twenty-seven of the fluoride/IQ studies are included in the meta-review by Choi, *supra* note 106. Studies published since Choi include: Das, *supra* note 21; Mondal D, et al. Inferring the fluoride hydrogeochemistry and effect of consuming fluoride-contaminated drinking water on human health in some endemic areas of Birbhum district, West Bengal. *Environmental Geochemistry & Health* 2016;38(2):557-76, attached as **Exhibit 139**; Zhang, *supra* note 94; Choi, *supra* note 107; Kundu H, et al. Effect of fluoride in drinking water on children's intelligence in high and low fluoride areas of Delhi. *Journal of the Indian Association of Public Health Dentistry* 2015;13(2):116-121, attached as **Exhibit 140**; Khan SA, et al. Relationship between dental fluorosis and intelligence quotient of school going children in and around Lucknow district: a cross-sectional study. *Journal of Clinical & Diagnostic Research* 2015;9(11):ZC10-15, attached as **Exhibit 141**, Bai Z, et al. Investigation and analysis of the development of intelligence levels and growth of children in areas suffering fluorine and arsenic toxicity from pollution from burning coal. Chinese Journal of Endemiology 2014;33(2):160-163, attached as **Exhibit 142**; Wei N, et al. The effects of comprehensive control measures on intelligence of school-age children in coal-burning-borne endemic fluorosis areas. *Chinese Journal of Endemiology* 2014;33(3):320-22 attached as **Exhibit 143**; Karimzade S, et al. Investigation of intelligence quotient in 9-12-year-old children exposed to high- and low-drinking water fluoride in West Azerbaijan province, Iran. *Fluoride* 2014;47(1):9-14 & 266-71, attached as **Exhibit 144**; Nagarajappa R, et al. Comparative assessment of intelligence quotient among children living in high and low fluoride areas of Kutch, India: a pilot study. *Iranian Journal of Public Health* 2013;2(8): 813–818, attached as **Exhibit 145**;

Trivedi MH, et al. Assessment of groundwater quality with special reference to fluoride and its impact on IQ of schoolchildren in six villages of the Mundra Region, Kachchh, Gujurat, India. *Fluoride* 2012;45(4):377-83, attached as **Exhibit 146**; Seraj B, et al. Effect of high water fluoride concentration on the intellectual development of children in Makoo/Iran. *Journal of Dentistry, Tehran University of Medical Sciences* 2012;9(3):221-29, attached as **Exhibit 147**; Ding Y, et al. The relationships between low levels of urine fluoride on children's intelligence, dental fluorosis in endemic fluorosis areas in Hulunbuir, Inner Mongolia, China. *Journal of Hazardous Materials* 2011;186(2-3):1942-46, attached as **Exhibit 148**; Poureslami HR, et al. Intelligence quotient of 7 to 9 year-old children from an area with high fluoride in drinking water. Journal of Dentistry and Oral Hygiene 2011;3(4):61-64, attached as **Exhibit 149**; Eswar P, et al. Intelligent quotients of 12-14 year old school children in a high and low fluoride village in India. *Fluoride* 2011;44:168-72, attached as **Exhibit 150**; Sudhir KM, et al. Effect of fluoride exposure on intelligence quotient (IQ) among 13-15 year old school children of known endemic area of fluorosis, Nalgonda District, Andhra Pradesh. *Journal of the Indian Association of Public Health Dentistry* 2009;13:88-94, attached as **Exhibit 151**; Li F, et al. The impact of endemic fluorosis caused by the burning of coal on the development of intelligence in children. *Journal of Environmental Health* 2009;26(4):838-40, attached as **Exhibit 152**. A complete list of the studies associating fluoride with reduced IQ is available at: http://fluoridealert.org/studies/brain01/. Petitioners can make all of these studies available to FDA upon request.

[110] Rocha Amador, *supra* note 106.

[111] Yazdi SM, et al. Effects of fluoride on psychomotor performance and memory of aluminum potroom workers. *Fluoride* 2011; 44:158-62, attached as **Exhibit 153**; Guo, *supra* note 108.

[112] We include here the animal studies that have been published in English (n=25): Zheng X, et al. Molecular mechanism of brain impairment caused by drinking-acquired fluorosis and selenium intervention. *Environmental Toxicology and Pharmacology* 2016;43:134-139, attached as **Exhibit 154**; Jetti R, et al. Protective effect of ascorbic acid and Ginkgo biloba against learning and memory deficits caused by fluoride. *Toxicology and Industrial Health* 2016;32(1):183-87, attached as **Exhibit 155**; Dong, *supra* note 106; Li M, et al. Pathologic changes and effect on the learning and memory ability in rats exposed to fluoride and aluminum. *Toxicology Research* 2015;4:1366-73, attached as **Exhibit 156**; Shalini B, Sharma JD. Beneficial effects of emblica officinalis on fluoride-induced toxicity on brain biochemical indexes and learning-memory in rats. T*oxicology International* 2015;22(1):35-9, attached as **Exhibit 157**; Balaji B, et al. Evaluation of standardized Bacopa monniera extract in sodium fluoride induced behavioural, biochemical, and histopathological alterations in mice. *Toxicology and Industrial Health* 2015;31(1):18-30, attached as **Exhibit 158**; Niu R, et al. Proteomic analysis of hippocampus in offspring male mice exposed to fluoride and lead. *Biological Trace Element Research* 2014;162(1-3):227-33, attached as **Exhibit 159**; Han, *supra* note 107; Jiang S, et al. Fluoride and arsenic exposure impairs learning and memory and decreases mGluR5 expression in the hippocampus and cortex in rats. *PLoS One* 2014;23;9(4):e96041, attached as **Exhibit 160**; Liu F, et al. Fluoride exposure during development affects both cognition and emotion in mice. *Physiology & Behavior* 2014;124:1-7, attached as **Exhibit 161**; Jiang C, et al. Low glucose utilization and neurodegenerative changes caused by sodium fluoride exposure in rat's developmental brain. *Neuromolecular Medicine* 2014;16(1):94-105, attached as **Exhibit 162**; Zhang C, et al. The analog of ginkgo biloba extract 761 is a protective factor of cognitive impairment induced by chronic fluorosis. *Biological Trace Element Research* 2013;153:229-36, attached as **Exhibit 163**; Basha PM, Sujitha NS. Combined impact of exercise and temperature in learning and memory performance of fluoride toxicated rats. *Biological Trace Element Research* 2012;150:306-13, attached as **Exhibit 164**; Pereira M, et al. Memory impairment induced by sodium fluoride is associated with changes in brain monoamine levels. *Neurotoxicity Research* 2011;19(1):55-62, attached as **Exhibit 165**; Basha PM, et al. Fluoride toxicity and status of serum thyroid hormones, brain histopathology, and learning memory in rats: a multigenerational assessment. *Biological Trace Element Research* 2011;144(1-3):1083-94, attached as **Exhibit 166**; Liu YJ, et al. Alterations of nAChRs and ERK1/2 in the brains of rats with chronic fluorosis and their connections with the decreased capacity of learning and memory. *Toxicology Letters* 2011;192(3):324-9, attached as **Exhibit 167**; Gui CZ, et al. Changes of learning and memory ability and brain nicotinic receptors of rat

offspring with coal burning fluorosis. *Neurotoxicology & Teratology* 2010;32(5):536-41, attached as **Exhibit 168**; El-Lethey H, et al. Neurobehavioral toxicity produced by sodium fluoride in drinking water of laboratory rats. *Journal of American Science* 2010;6:54-63, attached as **Exhibit 169**; Gao Q, et al. Decreased learning and memory ability in rats with fluorosis: increased oxidative stress and reduced cholinesterase activity in the brain. *Fluoride* 2009;42(4):277-85, attached as **Exhibit 170**; Niu *supra* note 97; Chioca LR, et al. Subchronic fluoride intake induces impairment in habituation and active avoidance tasks in rats. *European Journal of Pharmacology* 2008;579(1-3):196-201, attached as **Exhibit 171**; Wang J, et al. Effects of high fluoride and low iodine on biochemical indexes of the brain and learning-memory of offspring rats. *Fluoride* 2004;37:201-208, attached as **Exhibit 172**; Sun ZR, et al. Effects of high fluoride drinking water on the cerebral functions of mice. *Chinese Journal of Epidemiology* 2000;19: 262-263 (republished in *Fluoride* 2008;41:148-51), attached as **Exhibit 173;** Zhang Z, et al. Effect of fluoride exposure on synaptic structure of brain areas related to learning-memory in mice. *Journal of Hygiene Research* 1999;28(4):210-2 (republished in *Fluoride* 2008;41:139-43), attached as **Exhibit 174**.

[113] *See, e.g.*, Lin (1991), *supra* note 93, finding effect at **0.88 ppm**; Sudhir, *supra* note 109, finding effect at **0.7-1.2 ppm**; Zhang, *supra* note 94, finding effect at **1.4 ppm**; Xu Y, et al. The effect of fluorine on the level of intelligence in children. *Endemic Diseases Bulletin* 1994;9(2):83-84 (finding effect at **1.8 ppm**), attached as **Exhibit 175**; Xiang, *supra* note 106, finding effect at **1.9 ppm**; Ding, *supra* note 109, finding effect at **0.3-3.0 ppm**; Yao Y, et al. Comparative assessment of the physical and mental development of children in endemic fluorosis area with water improvement and without water improvement. *Literature and Information on Preventive Medicine* 1997;3(1):42-43 (finding effect at **2 ppm**), attached as **Exhibit 176**; Yao Y, et al. Analysis on TSH and intelligence level of children with dental fluorosis in a high fluoride area. *Literature and Information on Preventive Medicine* 1996;2(1):26-27 (finding effect at **2 ppm**), attached as **Exhibit 177**; Das, *supra* note 21, finding effect at **2.1 ppm**; Choi, *supra* note 107, finding effect at **2.2 ppm**; Trivedi, *supra* note 109, finding effect at **2.3 ppm**; Poureslami, *supra* note 109, finding effect at **2.38 ppm**; Nagarajappa, *supra* note 109, finding effect at **2.4-3.5 ppm**; Eswar, *supra* note 109, finding effect at **2.45 ppm**; Seraj, *supra* note 109, finding effect at **3.1 ppm**; Karimzade, *supra* note 109, finding effect at **3.94 ppm**. Although a recent study from New Zealand failed to detect a relationship between artificially fluoridated drinking water (1 ppm) and reduced IQ, the study had limited capacity to detect an effect due to the very narrow difference in fluoride intake between "exposed" and "non-exposed" communities. See Broadbent JM, et al. Community Water Fluoridation and Intelligence: Prospective Study in New Zealand. *American Journal of Public Health* 2015;105(1):72-76, attached as **Exhibit 178**; Osmunson B et al. Study incapable of detecting IQ loss from fluoride. *American Journal of Public Health* 2016;106(2):212-3, attached as **Exhibit 179.**

[114] Wong MCM, et al. Oral health status and oral health behaviors in Chinese children. *Journal of Dental Research* 2001;80(5):1459-65 (finding "low" availability and use of fluoride toothpaste in Chinese rural areas), attached as **Exhibit 180**.

[115] Ekstrand, *supra* note 70; *see also* Ekstrand J, et al. Fluoride pharmacokinetics in infancy. *Pediatric Research* 1994;35:157-63, Table 3 (finding that blood fluoride levels spike as high as 92 ppb among infants ingesting 0.25 mg F), attached as **Exhibit 181.**

[116] Mullenix, *supra* note 108.

[117] Feltman, *supra* note 23; see also Feltman R, Kosel G. Prenatal and postnatal ingestion of fluorides – Fourteen years of investigation – Final report. *Journal of Dental Medicine* 1961;16:190-99 ("One percent of our cases reacted adversely to the fluoride. . . . These reactions, occurring in gravid women and in children of all ages in the study group affected the dermatologic, gastro-intestinal and *neurological* systems."), attached as **Exhibit 182**.

[118] NRC, *supra* note 14, at 224-36, 260-63, 266-67. Research has repeatedly found that fluoride's neurological effects are sharply pronounced among human and animal populations with iodine deficiency. *See, e.g.*, Wang *supra* note 112; Wang X, et al. Effects of high iodine and high fluorine on children's intelligence and thyroid function. *Chinese Journal of Endemiology* 2001;20(4):288-90, attached as **Exhibit 183**; Hong F, et al. Research on the effects of fluoride on child intellectual development under different environments. *Chinese Primary*

Health Care 2001;15(3):56-57 (republished in *Fluoride* 2008; 41(2):156–60), attached as **Exhibit 184**; Xu *supra* note 113; Lin, *supra* note 93; Ren D, et al. A study of the intellectual ability of 8-14 year-old children in high fluoride, low iodine areas. Chinese Journal of Control of Endemic Diseases 4(4):251 (republished in Fluoride 2008; 41:319-20), attached as **Exhibit 185**; *see also* Ge Y, et al. Proteomic analysis of brain proteins of rats exposed to high fluoride and low iodine. *Archives of Toxicology* 2011;85(1):27-33, attached as **Exhibit 186**; Ge Y, et al. Comet assay of DNA damage in brain cells of adult rats exposed to high fluoride and low iodine. *Fluoride* 2005;38(3):209-14, attached as **Exhibit 187**.

[119] Galletti P, Joyet G. Effect of fluorine on thyroidal iodine metabolism in hyperthyroidism. *Journal of Clinical Endocrinology* 1958; 18(10):1102-1110, attached as **Exhibit 188**.

[120] According to the CDC's growth charts, the median weight of 3-year-old and 6-year-old girls is approximately 14 kg and 20 kg, respectively. See **Exhibit 189**. At these two ages, the recommended supplemental fluoride dose is 0.5 mg and 1.0 mg, respectively, which amounts to supplemental dosages of 0.036 mg/kg/day 0.050 mg/kg/day. In the Galletti hyperthyroidism trial, men and women of unknown weight between the ages of 27 and 57. Galletti, *supra* note 119, at 1104, Table 1. If we assume that these men and women had the average weight of a young adult (58 kg for women; 70 kg for men), their supplemental dosage from ingesting 5 mg fluoride (the most common dosage used in the study) would range from 0.071 mg/kg/day to 0.086 mg/kg/day. Thus, the difference in dosage between the two treatments is within a factor of two.

[121] *But see* Burgi H. Fluorine and thyroid gland function: a review of the literature. *Klin Wochenschr* 1984;62(12):564-9, at 567 (discussing a Swiss study which investigated occurrence of goiter among children ingesting 0.25 to 0.3 mg fluoride tablets for 20 months), attached as **Exhibit 190**.

[122] Peckham S, et al. 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* 2015;69(7):619-24, attached as **Exhibit 191.**

[123] *See* NRC, *supra* note 14, at 263 ("In humans, effects on thyroid function were associated with fluoride exposures of 0.05-0.13 mg/kg/day when iodine intake was adequate and 0.01-0.03 mg/kg/day when iodine intake was inadequate."); *see also id*. at 267 ("The effects of fluoride on various aspects of endocrine function should be examined further, particularly with respect to a possible role in the development of several diseases or mental states in the United States. Major areas for investigation include the following: thyroid disease (especially in light of decreasing iodine intake by the U.S. population) . . . .").

[124] NRC, *supra* note 14, at 256-67.

[125] Additional research has been published since the NRC's review in 2006 that further confirms a relationship between fluoride exposure and elevated blood glucose, including a study from China that was published in 2000, but not translated into English until 2012, that found high rates of glucose intolerance and diabetes among individuals living in a high-fluoride (8 ppm) area. *E.g.*, Xie YP, et al. Clinical study of the effect of high fluoride on the function of the pancreatic islet b-cells. *Chinese Journal of Endemiology* 2000;19(2): 84-6, attached as **Exhibit 192**. The research also includes studies published prior to 2006 that the NRC did not consider in its review. *E.g.*, Whitford GM, et al. Topical fluorides: effects on physiologic and biochemical processes. Journal of Dental Research 1987;66(5):1072-8, Table 2, attached as **Exhibit 193**; Shahed AR, et al. Effect of F on rat serum insulin levels in vivo. *Journal of Dental Research* 1986;65:756, attached as **Exhibit 194**.

[126] NRC, *supra* note 14, at 260.

[127] *Id.* at 260 ("In general, impaired glucose metabolism appears to be associated with serum or plasma fluoride concentrations of about 0.1 mg/L or greater in both animals and humans."). The following studies document effects of fluoride on glucose metabolism at 95 ppb (0.095 mg/L). Menoyo I, et al. Effect of fluoride on the secretion of insulin in the rat. *Arzneimittelforschung* 2005;55(5):455-60, attached as **Exhibit 195**; Rigalli A, et al. Inhibitory effect of fluoride on the secretion of insulin. *Calcified Tissue International* 1992;46:333-8, attached as **Exhibit 196**; Rigalli A, et al. Inhibitory effect of fluoride on the secretion of insulin. *Calcified Tissue International* 1990;46:333-8, attached as **Exhibit 197**.

[128] Ekstrand, *supra* note 70, at 380 Fig.1; *see also* Ekstrand, *supra* note 115 (finding that blood fluoride levels spike as high as 92 ppb among infants ingesting 0.25 mg F).
[129] Chiba FY, et al. NaF treatment increases TNF-a and resistin concentrations and reduces insulin signal in rats. *Journal of Fluorine Chemistry* 2012;136:3-7, at 6, attached as **Exhibit 198.**
[130] Ekstrand *supra* note 70; Ekstrand, *supra* note 115.
[131] *See, e.g.*, NRC, *supra* note 14, at 5 ("The weight of evidence indicates that, although fluoride might increase bone volume, there is less strength per unit volume."); Sogaard, *supra* note 15, at 166 ("[A]n overwhelming majority of the [animal] investigations mentioned found no effect or a negative effect of fluoride on bone strength…").
[132] NRC, *supra* note 14, at 165.
[133] *Id.* at 170 ("Overall, the committee finds that the available epidemiologic data for assessing bone fracture risk in relation to fluoride exposure around 2 mg/L is suggestive but inadequate for drawing firm conclusions about the risk or safety of exposures at that concentration.").
[134] Alarcon-Herrera, *supra* note 21.
[135] Levy SM, et al. Associations of fluoride intake with children's bone measures at age 11. *Community Dentistry & Oral Epidemiology* 2009;37(5):416-26, Table 4, attached as **Exhibit 199**.
[136] See Ekstrand, *supra* note 70 (showing that average blood fluoride spike in 3-to-4 years ingesting 0.5 mg F is 85 ppb); Ekstrand, *supra* note 115 (showing that average blood fluoride spike in infants ingesting 0.25 mg F is 63 ppb); Farley JR, et al. Fluoride directly stimulates proliferation and alkaline phosphatase activity of bone-forming cells. *Science* 1983;222(4621):330-2 (showing that fluoride alters bone cell activity at just 38 ppb in vitro), attached as **Exhibit 200**.
[137] Ferguson, *supra* note 23.
[138] Calcium deficiency is well-recognized as a factor that predisposes an individual to fluoride's toxic effects on mineralized tissues. *See, e.g.*, Simon, *supra* note 93; Teotia, *supra* note 93.
[139] See *supra* note 16 for supporting authorities.
[140] Bucher JR, et al. Results and conclusions of the National Toxicology Program's rodent carcinogenicity studies with sodium fluoride. *International Journal of Cancer* 1991;48(5):733-7, attached as **Exhibit 201.**
[141] Bassin EB, et al. Age-specific fluoride exposure in drinking water and osteosarcoma (United States). *Cancer Causes and Control* 2006;17:421-8, attached as **Exhibit 202**; Cohn PD. (1992). A Brief Report On The Association Of Drinking Water Fluoridation And The Incidence of Osteosarcoma Among Young Males. New Jersey Department of Health and Environmental Health Services , attached as **Exhibit 203**; Hoover RN, et al. (1991). Time trends for bone and joint cancers and osteosarcomas in the Surveillance, Epidemiology and End Results (SEER) Program. National Cancer Institute, attached as **Exhibit 204.**
[142] We have attached a review of these epidemiological studies as **Exhibit 205**. This review demonstrates that when the limitations of these studies are accounted for and corrected, "the current epidemiological evidence linking fluoride to childhood osteosarcoma is much stronger than currently recognized." Exhibit 206 also includes detailed analyses of the following studies that report no relationship between fluoride and osteosarcoma: Young N, et al. Community water fluoridation and health outcomes in England: a cross-sectional study. *Community Dent Oral Epidemiol.* 2015;43(6):550-9; Blakey K, et al. Is fluoride a risk factor for bone cancer? Small area analysis of osteosarcoma and Ewing sarcoma diagnosed among 0-49-year-olds in Great Britain, 1980-2005. *Int J Epidemiol .* 2014;43(1):224–234; Levy M, Leclerc BS. Fluoride in drinking water and osteosarcoma incidence rates in the continental United States among children and adolescents. *Cancer Epidemiol.* 2012;36(2):e83-8; Comber H, et al. Drinking water fluoridation and osteosarcoma incidence on the island of Ireland. *Cancer Causes Control.* 2011;22(6):919-24; Kim FM, et al. An assessment of bone fluoride and osteosarcoma. *J Dent Res .* 2011;90(10):1171–1176; Gelberg KH, et al. Fluoride exposure and childhood osteosarcoma a case-control study. *Am J Public Health .* 1995;85(12):1678–1683. These analyses show that "the Gelberg [1995], Kim [2011], and Blakey [2014] studies actually support the age-specific relationship between fluoride and osteosarcoma first identified by Bassin in 2006."
[143] Bassin, *supra* note 141.
[144] See *supra* notes 29-56 and accompanying text.

[145] Riordan, *supra* note 6, at 340.
[146] Burt, *supra* note 29, at 272.
[147] Tubert-Jeannin, *supra* note 11, at 2.
[148] See, for example, the labelling information for PureTek and Sancilio, *supra* note 66.
[149] See, for example, the labelling information for Libertas and Qualitest, *supra* note 66. See also the labeling materials provided by CVS to prospective customers of fluoride supplements, attached as **Exhibit 206**.
[150] See the labeling information provided by Rite Aid to prospective customers of fluoride supplements, attached as **Exhibit 207**.
[151] See the labeling information provided by Walgreens to prospective customers of fluoride supplements, attached as **Exhibit 208**.
[152] See the labeling information provided by Walmart to prospective customers of fluoride supplements, attached as **Exhibit 209**.
[153] See the labeling information provided by Rite Aid to prospective customers of fluoride supplements, *supra* note 150.
[154] See the labeling information provided by Libertas, PureTek, Qualitest, *supra* note 66, as well as the labeling information provided by CVS, Rite Aid, Walgreens, and Walmart, *supra* notes 149-53.
[155] See the labeling information provided by Sancilio, *supra* note 66.
[156] The labeling for both Qualitest and Libertas, *supra* note 66, summarize the study by Hennon, et al. as follows: "A comprehensive 5 1/2 year series of studies of the effectiveness of vitamin-fluoride products in caries protection has been published. Children in this continuing study lived in an area where the water supply contained only 0.05 ppm fluoride. The subjects were divided into two groups, one which used only non-fluoridated vitamin products and other vitamin-fluoride products. The three-year interim report showed 63% fewer carious surfaces in primary teeth and 43% fewer carious surfaces in permanent teeth of the children taking vitamin-fluoride products. After four years the studies continued to support the effectiveness of vitamin-fluoride products, showing a reduction in carious surfaces of 68% in primary teeth and 46% in permanent teeth. Results at the end of 5 1/2 years further confirmed the previous findings and indicated that significant reductions in dental caries are apparent with the continued use of vitamin-fluoride products." See labeling The Hennon trial was conducted in the 1960s.
[157] COMPLIANCE POLICY GUIDE, *supra* note 4, at 4 ("Such practices may be deliberate or done without adequate knowledge or understanding of the article.").
[158] 21 C.F.R. § 355.1 *et seq*.; Anticaries Drug Products for Over-the-Counter Human Use; Final Monograph, 60 Fed. Reg. 52474 (Oct. 6, 1995), at 52474 (discussing the procedural history of FDA's deliberations).
[159] 21 C.F.R. § 355.60.
[160] *Id.*
[161] All fluoride supplements sold on the market for caries prevention recommend that children aged 6 months to 3 years ingest 0.25 mg fluoride if they live in non-fluoridated areas. See labeling information cited *supra* note 66.
[162] COMPLIANCE POLICY GUIDE, *supra* note 4, at 5.
[163] *See* 21 U.S.C. § 355; 21 C.F.R. § 314.126.
[164] Riordan, *supra* note 6, at 335.
[165] Tomasin, *supra* note 38, at 4.
[166] See *supra* note 88 and accompanying text.
[167] Roberts, *supra* note 88.
[168] *Id.* at 3 ("It would be expected that pediatricians in an academic setting would be more up to date than those in private practice. So, if these knowledge gaps exist in academics, then the voids are likely to be larger among practitioners.").