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through the use of chemicals that alter the pH (acidity or alkalinity) of the tobacco. The effect is to promote tolerance and addiction in users.

The evidence of nicotine manipulation in smokeless tobacco in a manner that promotes tolerance in addiction in users is extensive. First, evidence shows that products intended for new users deliver less nicotine than products intended for experienced users. These graduated nicotine deliveries lead to increased tolerance and addiction because they allow new users to avoid adverse reactions to nicotine by beginning with low-nicotine products, while allowing experienced users to obtain sufficient nicotine to sustain their addiction by progressing to high-nicotine products.

Second, governmental data on smokeless tobacco use confirms that the graduated nicotine deliveries promote tolerance and addiction. These data show that since the advent of smokeless tobacco products with graduated nicotine deliveries, the number of children and adolescents who use and are addicted to smokeless tobacco has risen substantially.

Third, evidence from internal company documents and marketing campaigns of the nation's largest smokeless tobacco manufacturer, UST, shows the conscious manipulation of nicotine deliveries. UST deliberately relies on an explicit "graduation process" that introduces new users to low-nicotine delivery products while providing experienced users with higher-nicotine delivery products.

In combination with the evidence that the manufacturers understand the pharmacological effects and uses of nicotine, this evidence of nicotine manipulation to promote pharmacological effects in users demonstrates that the effects of nicotine in

smokeless tobacco on the structure and function of the body are "intended" by the manufacturers.

a. Evidence of Graduated Nicotine Deliveries

Absorption of a drug through the buccal mucosa in the mouth into the bloodstream can be increased or decreased by adjusting the pH of the drug. Pharmaceutical companies regularly alter pH by adding alkaline or acidic additives to drugs to increase or decrease their absorption into the bloodstream. Raising the pH converts many drugs from an ionized form into a non-ionized or "free" form that more readily crosses biological membranes.[1014]

Nicotine absorption is affected in this manner by pH levels. Increasing the pH of nicotine converts ionized nicotine into non-ionized nicotine, rendering it significantly more absorbable in the mouth.[1015] For this reason, the manufacturer of nicotine gum adds sodium carbonate to increase pH and enhance the absorption of nicotine.[1016] Tobacco industry-supported researchers have acknowledged that nicotine absorption in the mouth increases as a function of pH and that "the pharmacological response is clearly dependent on the amount of nicotine in the mouth as free base."[1017] Indeed, the senior vice president for marketing at

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[1014] Benet LZ, Steiner LB, Pharmacokinetics: The dynamics of drug absorption, distribution, and elimination in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (1990), 3-32, at 4-5. *See* AR (Vol. 711 Ref. 14).

[1015] Surgeon General's Report, 1988, at 29. *See* AR (Vol. 129 Ref. 1592).

[1016] Henningfield JE, Radzius A, Cooper TM, *et al.*, Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum, *Journal of the American Medical Association*, 1990;264:1560-1564. *See* AR (Vol. 29 Ref. 491-2).

[1017] Armitage AK, Turner DM, Absorption of nicotine in cigarette and cigar smoke through the oral mucosa, *Nature*, 1970;226:1231-1232, at 1232. *See* AR (Vol. 143 Ref. 1810).

Cholerton S, McCracken NW, Idle JR, Sources of inter-individual variability in nicotine pharmacokinetics, in *Nicotine and Related Alkaloids: Absorption, Distribution, Metabolism, and Excretion*, eds. Gorrod JW, Wahren J (1993), at 220-221 ("Absorption of nicotine from chewing tobacco and nicotine gum is facilitated by buffering of the preparations to an alkaline pH (approx. 8.5)"). *See* AR (Vol. 47 Ref. 70).

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UST conceded that it was his understanding that "if the pH of the snuff product is raised, . . . the rate of absorption of the nicotine would be increased in the user's mouth."[1018]

The data collected and analyzed by FDA[1019] and others[1020] demonstrate that moist snuff products marketed as "starter" products have relatively low pH levels, while products for established users have significantly higher pH levels, resulting in a pattern of graduated delivery of free nicotine. UST's principal line of starter products is its "Skoal Bandits" line. The pH levels for Skoal Bandits are low, ranging from 5.2 to 5.6 for Skoal Bandits Classic to 6.8 to 7.1 for Skoal Bandits Mint; the free nicotine provided by Skoal Bandits is also low, ranging from 0.2% to 0.4% for Skoal Bandits Classic to only 6.4% to 9.9% for Skoal Bandits Mint. *See* Jurisdictional Analysis, 60 FR 41737. Likewise, another UST starter product, "Happy Days," has a pH of 6.0 and provides only 0.9% free nicotine. In contrast, UST's principal product for established users, Copenhagen, has a pH of 7.7 to 8.1. Because pH is measured on a logarithmic scale, the alkalinity of Copenhagen is approximately two

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[1018] The exchange from the *Marsee* trial transcript on this point was:

> Q: And correspondingly, if the pH of the snuff product is raised, then, the rate of absorption of the nicotine from the snuff product would be increased in the user's mouth?
> A: Although I am not an expert on this, that is to the best of my understanding correct.

Deposition of Erik Lindqvist, *Marsee v. U.S. Tobacco,* Civil Action No. 84-2777R (W.R. Ok. 1986). Transcript of jury trial proceedings, at 1668. *See* AR (Vol. 29 Ref. 489-2).The relationship between ionized nicotine and nicotine in its free form is thus similar to the relationship between cocaine and "free-base" or "crack" cocaine. Increasing the pH of cocaine, through the addition of alkaline additives such as sodium bicarbonate and ammonia, converts cocaine salt into free-base or crack cocaine, thereby significantly increasing the rate at which the cocaine is absorbed into the bloodstream. Siegel RK, Part III cocaine free base use, *Journal of Psychoactive Drugs* 1982;14:311-318, 352-359. *See* AR (Vol. 711 Ref. 23).

[1019] The table on the next page presents the results of the studies performed by the two FDA laboratories in St. Louis, Missouri, and Cincinnati, Ohio.

[1020] Djordjevic MV, Hoffmann D, Glynn T, *et al.*, US commercial brands of moist snuff, 1994, Assessment of nicotine, moisture, and pH, *Tobacco Control,* 1995;4:62-66. *See* AR (Vol. 528 Ref. 97, appendix 9).

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TOTAL NICOTINE

MANUFACTURER/ PRODUCT NAME	pH		% Free Nicotine*		Content(mg/gm)**	
	St.Louis	Cinc.	St.Louis	Cinc.	St. Louis	Cinc.
U.S. Tobacco Co.						
Skoal Key	-	8.22	-	61.3	-	12.4
Copenhagen Snuff	8.14	7.71	56.5	32.7	13.2	13.8
Skoal L.C. Class	8.04	7.92	51.1	44.5	12.7	13.8
Skoal L.C. Wint.	7.50	7.57	23.1	26.0	12.7	13.9
Skoal L.C. Mint	7.35	7.52	17.6	24.0	13.2	13.7
Skoal L.C. Spear.	7.20	7.50	14.0	23.3	12.5	13.8
Skoal Or.F.C. Wint.	-	7.41	-	19.7	-	13.6
Skoal L.C. Strai.	7.47	7.41	22.0	19.5	12.1	13.8
Skoal L.C. Cherry	7.15	7.38	12.3	18.5	12.5	13.6
Skoal Band. Mint	6.83	7.06	6.4	9.9	6.7	8.8
Skoal Band. Wint.	6.56	6.72	3.3	4.8	7.8	8.2
Happy Days L.C. Mint -	6.00	-	0.9	-	13.9	
Skoal Band. Strai.	-	5.48	-	0.3	-	10.8
Skoal Band. Class.	5.61	5.23	0.39	0.2	10.4	9.9
Helme Tobacco Co.* **						
Redwood Full Flavor	-	7.52	-	24.0	-	12.6
Silver Cr. L.C.	-	7.22	-	13.7	-	6.0
Cooper Wint. L.C.	-	6.99	-	8.5	-	5.7
Gold River L.C.	-	5.77	-	0.6	-	6.4
Conwood Co.						
Kodiak Wint.	8.20	8.22	59.9	61.0	11.4	11.7
Kodiak Choice Wint.	-	7.98	-	47.7	-	11.4
Kodiak Straight	7.39	7.82	19.0	38.4	10.6	10.4
Hawken Wint.	5.56	5.58	0.35	0.4	4.4	0.4
Pinkerton Tobacco Co.						
Redman F.C. Ex. Wint.	-	7.58	-	-	-	12.3
Renegade Wint.	6.81	7.17	5.8	-	13.2	11.8

L.C. = long cut

* Calculated using the Henderson-Hasselbach Equation for acid base equilibrium. This calculation strictly is dependent on the pH determination. Any error in the pH determination will affect the percent free nicotine calculation.

** Measured on wet basis

*** Now Swisher International, Inc.

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orders of magnitude higher than the alkalinity of Skoal Bandits Classic and Happy Days (as measured in hydrogen ion concentrations). The level of free nicotine provided by Copenhagen is 33% to 57%, also far higher than the levels provided by Skoal Bandits or Happy Days.[1021]

The same pattern of graduated nicotine deliveries is found in the smokeless tobacco products of other manufacturers. Conwood's principal line of moist snuff starter products, "Hawken," has a pH of 5.6 and provides 0.4% free nicotine, whereas Conwood's product marketed for established users, "Kodiak-Wintergreen," has a pH of 8.2 and provides about 60% free nicotine.[1022] Similarly, the principal starter product of Swisher International, Inc. (formerly Helme Tobacco Co.), "Gold River L.C.," has a pH of 5.8 and provides 0.6% free nicotine, whereas its product marketed for established users, "Redwood Full Flavor," has a pH of 7.5 and provides 24% free nicotine.[1023]

These graduated nicotine deliveries directly promote tolerance and addiction. New users of smokeless tobacco have not developed a tolerance to nicotine. As a result, as a UST study documented, too much nicotine causes adverse reactions such as nausea and vomiting in new users,[1024] discouraging future experimentation with smokeless tobacco. Once tolerance to nicotine is developed, however, increasing doses of nicotine are required to

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[1021] *See* Table of "Total Nicotine" above.

[1022] *Id.*

[1023] *Id.*

[1024] U.S. Tobacco Company, Pharmacokinetics of Nicotine and Its Major Metabolites in Naive and Habituated Snuff Takers, Plaintiff's exhibit 3.27 from *Marsee v. U.S. Tobacco,* Civil Action No. 84-2777R (W.D. Ok. 1986), at 9. *See* AR (Vol. 24 Ref. 317).

produce the desired pharmacological effects.[1025] Thus, if nicotine levels were kept uniformly low to accommodate new users, the experienced user would not obtain the higher level of nicotine delivery needed to satisfy the user's addiction and to provide other desired pharmacological effects.

Graduating nicotine deliveries avoid these consequences and lead to increased tolerance and addiction. The low levels of nicotine delivery in starter brands, such as Skoal Bandits, allow the new user to develop a tolerance to nicotine[1026] without nausea and other adverse reactions. Once this tolerance is developed, the high levels of nicotine delivery in brands such as Copenhagen provide the experienced user with the desired increase in nicotine dose. Nicotine addiction is the final result.

There are several techniques the smokeless manufacturers use to achieve control over pH levels in smokeless tobacco. According to one report, pH adjustment is "done through fermentation, by adding alkaline buffering agents such as sodium carbonate and ammonium carbonate, or by altering the moisture content."[1027] The Swedish Tobacco Company, which like Pinkerton Tobacco Company is owned by Procordia AB, has admitted that "*[i]n order to release the nicotine from the tobacco, the snuff is made slightly alkaline—sodium carbonate is added. . . .*"[1028] The Smokeless Tobacco Council has also reported that two alkaline

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[1025] Surgeon General's Report, 1988, at 44-45. *See* AR (Vol. 129 Ref. 1592).

[1026] Connolly GN, Orleans CT, Blum A, Snuffing tobacco out of sport, *American Journal of Public Health* Mar. 1992;82(3):352. *See* AR (Vol. 94 Ref. 629).

[1027] Connolly GN, Marketing of Nicotine Addiction By One Oral Snuff Manufacturer, *Tobacco Control* 1995;4:73-79, at 74. *See* AR (Vol. 528 Ref. 97, appendix 9).

[1028] Swedish Tobacco Company, Smokeless Tobacco from Gothenburg, 1994, appendix B, quoted in statement of Gregory N. Connolly in *Health Effects of Smokeless Tobacco: Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 53 (Nov. 29, 1994) (emphasis added). *See* AR (Vol. 710 Ref. 4).

buffering agents, sodium carbonate and ammonium carbonate, are used in smokeless tobacco sold in the U.S.[1029]

Despite this evidence, the smokeless tobacco industry argues that the pattern of pH values in smokeless tobacco is not the result of intentional nicotine manipulation. The Agency disagrees. The pH values in the upper ranges seen in marketed smokeless tobacco for established users do not occur naturally in the tobacco used for the production of smokeless tobacco. Jack Henningfield, chief, clinical pharmacology branch of the Addiction Research Center at the National Institute on Drug Abuse, testified before Congress:

> Naturally occurring tobacco . . . does not occur, at least in these kinds of tobaccos, at the high pH levels that we observed. Normal fermentation processes typically result in acidification, as anyone has found when they saw their wine turn into vinegar. But here we see very high [alkaline] pH levels in some of the products.[1030]

Moreover, other product features reflect a consistent attempt to market products that deliver smaller amounts of nicotine to new users and products that deliver larger amounts to established users. For example, UST's Skoal Bandits and Pinkerton's starter product, Renegades, are packaged in teabag-like pouches, which both contain a much smaller amount of snuff (about 0.5g) than the usual standard size "pinch" of snuff (about 1.5g). The pouch system also delays the release of nicotine from the snuff.[1031] Thus, FDA data show that,

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[1029] Letter to Waxman HA and Bliley, Jr. TJ (U. S. House of Representatives) from Pape SM (Patton, Boggs & Blow) (May 3, 1994), with enclosure *Ingredients Added to Tobacco in the Manufacture of Smokeless Tobacco Products as of April 4, 1994. See* AR (Vol. 192 Ref. 2173).

[1030] *Health Effects of Smokeless Tobacco: Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives,* 103d Cong., 2d Sess. 98 (Nov. 29, 1994) (statement of Jack Henningfield). *See* AR (Vol. 710 Ref. 4).

[1031] Memorandum from Ciolino L, *Moist Snuff Nicotine Release Studies* (Sep. 28, 1994), at 1. *See* AR (Vol. 30 Ref. 500-2).

under typical use conditions, a standard size "pinch" of Copenhagen releases *12 times as much nicotine* in the first 2 minutes as a pouch of Bandits.[1032]

The evidence thus demonstrates that smokeless tobacco manufacturers intentionally manipulate the pH levels of smokeless tobacco, thereby controlling and adjusting the level of nicotine delivered to consumers. Products intended for new users have uniformly lower levels of pH and nicotine delivery than products intended for experienced users. The effect is to promote nicotine tolerance and addiction in users of smokeless tobacco.

b. Evidence that Teenage Users Graduate from Smokeless Tobacco with Low Nicotine Deliveries to Products with High Nicotine Deliveries

Data on teenage use of smokeless tobacco shows that the manufacturers' graduated nicotine deliveries have increased addiction to smokeless tobacco among young people. These data show that: (1) children and adolescents begin smokeless tobacco use with low nicotine delivery starter products and then switch to products with higher nicotine deliveries; and (2) the number of children and adolescents addicted to smokeless tobacco has risen substantially since the introduction of smokeless tobacco products with graduated nicotine deliveries.

Before the introduction of starter brands with low levels of nicotine in the early 1970's, virtually no teenagers and young adults used smokeless tobacco. According to the Centers for Disease Control and Prevention (CDC), "[i]n 1970, the use of smokeless tobacco

[1032] *Id.* at 2. *See* AR (Vol. 30 Ref. 500-2).

was a behavior primarily restricted to older men."[1033] In that year, only 2.2% of young males used smokeless tobacco, compared with 12.7% of males age 65 or older.[1034]

In the 1970's, however, smokeless tobacco manufacturers began to market low-nicotine "starter" products.[1035] These products have proven extremely successful in attracting young new users. Use by adolescent males aged 18 to 19 has increased approximately 1,500% between 1971 and 1991.[1036] Overall, use of smokeless tobacco almost tripled between 1970 and 1991.[1037] As discussed in section II.B.2., above, it has been estimated that approximately 75% of the regular young users of smokeless tobacco are addicted to nicotine.

Although the majority of the industry's advertising dollars are spent on promoting low- and medium-nicotine brands,[1038] these brands serve mainly as a stepping stone to the high-nicotine delivery products. Most of the increased sales of smokeless tobacco are sales of high-nicotine delivery brands, like Copenhagen.[1039]

[1033] *Health Effects of Smokeless Tobacco: Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 34 (Nov. 29, 1994) (statement of Michael P. Eriksen). *See* AR (Vol. 710 Ref. 4).

[1034] *Id.*

[1035] Connolly GN, *In the search for a perfect starter product: manipulation of nicotine in oral snuff brands* (1994) (unpublished), at 3-4. *See* AR (Vol. 30 Ref. 511).

[1036] Centers for Disease Control and Prevention, Office of Smoking and Health, unpublished data from 1970 and 1991 National Household Interview Surveys (rate of snuff use among 18-19 year-old males was 0.5% in 1970 and 7.6% in 1991). *See* AR (Vol. 31 Ref. 521-1).

[1037] *Id.*

[1038] Connolly GN, *In the search for a perfect starter product: manipulation of nicotine in oral snuff brands* (1994) (unpublished), at 5. *See* AR (Vol. 30 Ref. 511).

[1039] *Id.* at 6.

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A study by CDC confirms the role of low-nicotine delivery brands as starter products. The study analyzes data from CDC's 1993 Teenage Attitudes and Practices Survey (TAPS) and from a follow-up study to the 1989 TAPS.[1040] The authors found that the percentage of beginning teenage snuff users who bought Skoal Bandits (low nicotine delivery) and Skoal (medium nicotine delivery) was higher than the percentage of experienced teenage snuff users who bought these products.[1041] Similarly, the proportion of teenage snuff users who chose Copenhagen (high nicotine delivery) was about three times higher among those who used snuff for 4 years or more than among those who used snuff for 1 year or less.[1042] Use of Copenhagen was also higher among those who used smokeless tobacco more frequently and with increased intensity.[1043] The study also included an analysis that found that of those who used Skoal Bandits or Skoal at the beginning of the study, nearly a third had switched to Copenhagen 4 years later.[1044] However, among those who used Copenhagen at the beginning of the study, 83% were still using it 4 years later. Thus, teenage moist snuff users were significantly more likely to graduate to a higher nicotine delivery product than to switch down to a lower nicotine delivery product.[1045]

The CDC report concluded that these findings "support the hypothesis that snuff users in earlier stages of tobacco use and nicotine addiction, use brands with low levels of

[1040] Tomar S, Giovino G, Eriksen M, Smokeless tobacco brand preference and switching among U.S. adolescents and young adults, *Tobacco Control* 1995;4:67-72. *See* AR (Vol. 528 Ref. 97, appendix 9).

[1041] *Id.* at 69.

[1042] *Id.* at 71.

[1043] *Id.*

[1044] *Id.*

[1045] *Id.*