The undersigned submit this petition pursuant to Title 21, Chapter 9, Subchapter V, Part A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 10.30 to request the Commissioner of the Food and Drug Administration to alter the manner in which the agency reviews drug approval applications for and regulates nicotine replacement therapy medications. Specific changes to the packaging label and warnings are set forth in detail at the end of this Petition. In addition to the text of this Petition, the undersigned submit *Barriers to Use of FDA-Approved Smoking Cessation Medications: Implications for Policy Action*, a study funded by the Robert Woods Johnson Foundation and the Society for Research on Nicotine and Tobacco, in support of the request.

I. PRELIMINARY STATEMENT

Cigarette smoking presents a complex and deep-rooted public health dilemma in the United States. We lose hundreds of thousands of lives and millions more Americans suffer painful and life-altering health consequences as a result of smoking. The economic toll of the suffering is tremendous. Yet all of the suffering and economic loss is preventable. To eliminate the public health crisis presented by smoking, federal, state and local health authorities dedicate significant resources to prevent tobacco use initiation and to increase cessation. In fact, the federal government, through the Centers for Disease Control (CDC), has established a goal of reducing the adult smoking rate to 12% by 2010.[1] Recent data indicate that the U.S. will fall far short of that goal, making ready access to effective and safe cessation aids even more crucial in the coming years.[2] All government agencies and officials should be mindful of these imperatives when developing, implementing and applying policies and laws that relate to tobacco use or cessation.

Smoking cessation is a difficult goal both for the individual smoker, public health agencies, and other treatment providers seeking to increase successful cessation at the population level. Research makes clear that a multi-faceted approach to cessation is necessary and that treatment of nicotine dependence using nicotine replacement therapy (NRT) is an important part of the quitting process for

[1] Healthy People 2010, Centers for Disease Control, chapter 27: Tobacco Use (available at http://www.healthypeople.gov/document/html/volume2/27tobacco.htm).

[2] Centers for Disease Control, *Cigarette Smoking Among Adults, 2007*, MMWR, 57:1221-1248 (November 14, 2008)(assessing adult smoking prevalence at 19.8 percent or 43.4 million people). "Smokers should be aware that there are treatments and services available to help them quit now more than ever before. Smokers can more than double their likelihood of successfully quitting by using medications and telephone counseling." Press Release, *Slightly Lower Adult Smoking Rates*, Centers for Disease Control (November 13, 2008)(quoting Janet Collins, PhD, Director of CDC's National Center for Chronic Disease Prevention and Health Promotion). *See also* "A Call for ACTTION: Access to Cessation Treatment for Tobacco in Our Nation," Partnership for Prevention (November 2008)(available at http://www.acttiontoquit.org/uploads/documents/call_for_action.pdf). This document was released by the Partnership in coordination and cooperation with federal agencies, leading public health organizations and former public health officials and presents an action plan for increasing access to tobacco-use treatment.

many smokers.[3] Use of NRT during the quitting process diminishes the craving and discomfort of nicotine withdrawal and makes short-term and long-term success more likely. Barriers to the use of NRT must be diminished while access to NRT must improve to increase the number of successful quit attempts. Included in access is assuring that individuals considering smoking cessation fully appreciate both the profoundly negative risks of continued smoking and the significantly lower risks of using NRT. Smokers' confusion or misunderstanding about the risks presented by use of NRT contribute to reduced use of effective medicines by individuals and ultimately retard efforts of public health agencies and organizations working to reduce smoking in the population. Confusion and misunderstanding by medical professionals compounds this problem. In addition, the high cost of NRT and limited packaging options make NRT less accessible and therefore used less frequently and less effectively.

Tight constraints imposed by the Food and Drug Administration ("FDA") on manufacturers of NRT interfere with full and effective use of NRT by individuals and across the population. These constraints conflict with the clear evidence that use of NRT in almost all populations is tremendously safer than smoking, which is an appropriate reference point for assessing the efficacy and safety of NRT. The agency should bear in mind that the essential ingredient in NRT is not a new substance for those who choose to use the medication; rather, NRT is a far safer method of delivering the nicotine on which smokers are already dependent.

II. ACTION REQUESTED

Petitioners urge the FDA to adopt principles that will allow the agency to review packaging and labeling requirements for, and retail availability of, NRT with consideration of the individual and public health impact of diminished smoking. The FDA should also be mindful of the risks of continued smoking and weigh those risks when deciding whether to approve a new or modified NRT product and when determining what restrictions should be imposed on the use, retail sale, packaging and labeling of such products. When regulating NRT, the FDA should consider the significant impact of smoking on individuals and the population and take action consistent with the goal of enhancing cessation efforts by making NRT as widely available as safely possible. As explained and supported in the attached report, *Barriers to Use of FDA-Approved Smoking Cessation Medications: Implications for Policy Action*, regulation of NRT products should be made by comparing the risk of NRT use not only with the risk of placebo or no NRT but with continued smoking.[4]

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[3] Throughout this Petition, the term nicotine replacement therapy, or NRT, includes various medications approved by the Food and Drug Administration for the treatment of the symptoms of nicotine withdrawal. These include the nicotine patch, gum, lozenge, nasal spray, and inhaler. Other medications designed to assist with smoking cessation but not containing nicotine, such as varenicline or bupropion, are not included in the term NRT and not specifically addressed in this Petition.

[4] *Barriers to Use of FDA-Approved Smoking Cessation Medications: Implications for Policy Action* at pp. 15-16. This document was created pursuant to a grant from the Robert Woods Johnson Foundation and the Society for Research on Nicotine and Tobacco. Dr. Jonathan Foulds served as Principal Investigator and eleven public health

Specifically, Petitioners request the following actions be taken. Support for these actions and further explanation is provided in the body of the Petition and in the Barriers Report.

1) ***Comparison of Health Risks*:** The FDA must recognize and use as a guiding principle that tobacco dependence is a chronic disease, one that causes other grave illness and often death in smokers. The magnitude of the risk of continued smoking should be considered at all phases of review of NRT products. On NRT products approved as safe and effective, product labeling should reflect the potential health risks associated with use of NRT as compared to the significant negative health risks caused by smoking. This comparison is the appropriate measure as it should be assumed that the consumer considering NRT is currently smoking and plans to reduce or quit smoking by using NRT.

2) ***Combined Use*:** Package labeling should allow for combined use of NRT products. Current labeling strongly warns against the combined use of NRT products yet sound research shows that combined use is safe and highly effective. Labeling should reflect that certain NRT products may be used safely and effectively in combination rather than that such use is prohibited or discouraged.

3) ***Term of Treatment*:** NRT users should not be discouraged from using the product beyond the currently recommended 10 to 12 weeks. Research supports that use well beyond 12 weeks is safe and may be more effective in achieving full and permanent smoking cessation for some individuals than the standard shorter course of treatment. Current labeling instructing that NRT use stop at 10 or 12 weeks should be amended.

4) ***Package Size*:** To enhance accessibility, the FDA should permit the sale of NRT in one-day packages that can be priced affordably. Currently the FDA prohibits such packaging. The high price of NRT under current packaging standards, particularly as compared to the much lower price of a package of cigarettes, discourages quit attempts and smoking cessation.

5) ***Continued Smoking and NRT*:** Package labeling strongly warning against continued smoking and use of NRT should be amended such that consumers are encouraged to use NRT to treat the symptoms of nicotine withdrawal during temporary smoking abstinence or to assist consumers in reducing cigarette consumption prior to complete cessation.

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and tobacco research experts contributed to the Report. Throughout this Petition, the document will be referred to as the Barriers Report. Specific advice for consumers on the use of NRT is available in Appendix A of the Barriers Report. In Appendix B, Principles for Regulating Medicines Designed to Treat Tobacco Dependence, the authors provide concrete approaches the FDA and other agencies should consider when addressing issues related to the treatment of tobacco dependence. *See also* "Increasing Access to Effective Treatments: The Case for More Flexible Regulatory Policy," Pre-Symposium Conference, Society for Research on Nicotine and Tobacco (February 2007)(presentations available at http://roswelldocs.com/srnt.htm).

6) ***Availability of NRT at Retail Stores*****:** NRT should be available as widely as possible. The FDA should explicitly remove any restrictions that discourage the sale of NRT at non-pharmacy retail locations; NRT should be widely available at retail establishments, including all stores where cigarettes are sold.

7) ***NRT Use by Certain Populations*****:** Current warnings inappropriately discourage individuals with certain health conditions from using NRT. The FDA should modify the required warnings to encourage smoking reduction or cessation by individuals suffering from heart disease and other smoking-related chronic conditions.

III. STATEMENT OF GROUNDS

THE FDA SHOULD APPROACH THE REGULATION OF NRT WITH THE PRINCIPAL GOAL OF REDUCING THE DEVASTATING HEALTH CONSEQUENCES OF SMOKING

Smoking continues to be a public health crisis of epic proportion. Every public and private agency tasked with improving public health should be aggressive and dynamic in working to reduce the significant negative health consequences associated with smoking. For the FDA, this means, in part, encouraging the development and marketing of medications designed to reduce smoking and regulating the availability and labeling of such medications to increase accessibility and promote safe and effective use. Adopting regulatory principles that reflect an understanding of the profound public health harm caused by smoking should cause the FDA to loosen current restrictions that are interfering with safe and effective use of NRT. Being mindful that the proper framework compares the use of NRT against continued smoking should result in increased access to and effective use of NRT.

A. THE PUBLIC HEALTH AND ECONOMIC IMPACT OF SMOKING IS DEVASTATING AND SHOULD BE CONSIDERED BY THE FDA WHEN REGULATING NRT

Smoking is the leading cause of preventable death in the United States.[5] About one in five adults in the United States smokes cigarettes; that is about 43.4 million American smokers.[6] Cigarette smoking kills more than 440,000 Americans each year.[7] The most recent Surgeon General Report to address the health consequences of smoking details in more than 900 pages the devastating toll of smoking, concluding that smoking negatively affects nearly every organ in the body and causes innumerable dreadful illnesses, including various forms of cancer, cardiovascular disease, respiratory disease, reproductive concerns, and much more.[8] In addition to making ill and killing hundreds of thousands of Americans each year, smoking costs approximately $157 billion in annual health costs.[9] The Surgeon General intended his report to serve as an "impetus for even more vigorous programs to reduce and prevent smoking" and concluded that "smokers who quit can lower their risk of smoking-caused

[5] *The Health Consequences of Smoking*, A Report of the Surgeon General (2004)(hereafter SGR 2004) (Executive Summary at page 14; Chapter 7; page 861).

[6] Centers for Disease Control, *Cigarette Smoking Among Adults, 2007*, MMWR, 57:1221-1226 (November 14, 2008)(adult smoking prevalence, 19.8%).

[7] SGR 2004 (Chapter 7, page 858 and Table 7.3).

[8] SGR 2004. The Report is supported by more than 16,000 reliable scientific reports and studies. One of the major conclusions is that "[s]moking harms nearly every organ of the body, causing many diseases and reducing the health of smokers in general." Executive Summary at 8.

[9] SGR 2004 (Chapter 7, page 869, Table 7.8).

diseases and improve their health status generally."[10] Therefore, getting smokers to quit should be the mission of every health-related agency at the federal, state and local level. NRT can and should play a role in those efforts. For the FDA, this means that when regulating NRT, the agency should develop and implement a framework that considers the severe public health and economic costs of smoking in relation to the minimal risk of NRT use and the public health and economic gains achieved by increased cessation.

B. Nicotine Replacement Therapy is Safe and Effective in Assisting Smokers to Reduce or Stop Smoking Even When Used Outside of Current Product Labeling

Anecdotally, former smokers and smokers who have tried to quit tell a harrowing story of the physical, emotional and psychological effects of nicotine withdrawal. The fact that nicotine withdrawal creates significant symptoms is recognized by the American Psychiatric Association, which identifies nicotine withdrawal as a disorder.[11] Symptoms of nicotine withdrawal include depression, anxiety, irritability, difficulty concentrating, insomnia, restlessness, headache, and weight gain.[12] Worst of all, withdrawal symptoms cause most smokers attempting to quit to return to daily smoking. The habitual nature and social aspects of smoking also make cessation difficult. In fact, it is fair to consider tobacco dependence a chronic disease as "the majority of users persist in tobacco use for many years and typically cycle through multiple periods of remission and relapse."[13] Hence, each year although more than 70 percent of smokers want to quit, only 44 percent actually attempt to quit and only about 4 to 7 percent succeed.[14] These are discouraging numbers that should compel public health officials to take action to improve the quit rate among smokers.

Increased access to effective NRT is one element of improving the likelihood that a smoker will succeed in quitting because, even though availability is currently constrained, NRT contributes positively

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[10] SGR 2004 (Executive Summary at page 7); *see also* Executive Summary, Major Conclusions (page 8)("Quitting smoking has immediate as well as long-term benefits, reducing risk for diseases caused by smoking and improving health in general.").

[11] DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, 4th Ed. (Text Revision), American Psychiatric Association: Wash., D.C. (2000) at 244-47.

[12] *The Health Consequences of Smoking: Nicotine Addiction*, A Report of the Surgeon General (1988); *see also* J. Hughes, *et al.*, *Effects of Abstinence from Tobacco*, in RECENT ADVANCES IN ALCOHOL AND DRUG PROBLEMS at 10 (Plenum; New York, 1990); M. Al' Absi, *et al.*, *Psychophysiologic Effects of Nicotine Abstinence and Behavioral Changes in Habitual Smokers*, 72 PHARMACOL. BIOCHEM. BEHAV.707 (2002).

[13] Department of Health and Human Services, Public Health Service, TREATING TOBACCO USE AND DEPENDENCE: CLINICAL PRACTICE GUIDELINE (Updated 2008)(hereafter CPG) at 15.

[14] Centers for Disease Control, *Cigarette Smoking Among Adults, 2006*, MMWR, 56:1157-61 (2007); *see also* J. Hughes, *et al., Shape of the relapse curve and long-term abstinence among untreated smokers*, 92 ADDICTION 29 (2004).

to quit rates.[15] Use of NRT during a quit attempt increases by 50 to 70 percent the likelihood of success.[16] More than a hundred randomized controlled trials in over 40,000 patients present significant evidence of the efficacy of NRT in tobacco cessation.[17] A recent study confirms the effectiveness of NRT: Smokers who spontaneously chose to quit and used NRT experienced 2.2 times the odds of reporting no tobacco use 6 months after the quit date as compared to those not using NRT.[18] That NRT is efficacious in assisting with smoking cessation is evident from the FDA's approval of many forms and brands of NRT for use in cessation as a critical element required for FDA approval is efficacy.[19] Moreover, the Public Health Service (PHS) of the Department of Health and Human Services clearly recognizes the positive impact of NRT on tobacco cessation in the agency's Clinical Practice Guideline.[20] The Guideline identifies seven primary medications helpful to smoking cessation: bupropion SR, nicotine gum, nicotine inhaler, nicotine lozenges, nicotine nasal spray, nicotine patch, and varenicline. "Each has been documented to increase significantly rates of long-term smoking abstinence."[21] Therefore, for every patient who

[15] For a brief history of NRT, see Barriers Report at 13.

[16] L. Stead, *et al.*, *Nicotine replacement therapy for smoking cessation*, COCHRANE DATABASE OF SYSTEMATIC REVIEW, Issue 4 (January 23, 2008)(hereafter Stead (Cochrane)).

[17] Stead (Cochrane); *see also* M. Eisenberg, *et al.*, *Pharmocatherapies for smoking cessation: a meta-analysis of randomized controlled trials*, 179 CANADIAN MEDICAL ASSOCIATION JOURNAL 135 (July 2008).

[18] R. West and X. Zhou, *Is nicotine replacement therapy for smoking cessation effective in the "real world"? Findings from a prospective multinational cohort study*, 62 THORAX 998 (November 2007)(study controlled for baseline nicotine dependence and also found that smokers who used non-NRT aids such as hypnotism and acupuncture were no more likely to succeed than those not using such an aid); *see also* Piper, *et al*., *A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies*, 66 ARCH. GEN. PSYCHIATRY 1253 (November 2009)(finding 5 pharmacotherapies, including the patch efficacious).

[19] *See* 21 U.S.C. §355 (new drug approval process; FDCA §505); 21 C.F.R. §314.105(c)("FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness . . . .").

[20] CPG at 108 ("The first-line medications have an established empirical record of effectiveness, and clinicians should consider these agents first in choosing a medication.").

[21] CPG at 106; *see also* Barriers Report at 5 ("The evidence for the efficacy of currently approved pharmacological treatments [for smoking cessation] is extensive, and is based on more than a hundred randomized controlled trials in over 40,000 patients."). This Petition does not address directly the non-NRT smoking cessation medications, such as varenicline or bupropion. But the principles espoused herein certainly apply to the approval process of all drugs that can safely and effectively assist in smoking cessation.

expresses a desire to quit smoking, the Guideline suggests that a clinician recommend use of an approved tobacco cessation treatment medication, unless contraindicated.[22]

That the FDA has approved NRT products and that the Clinical Practice Guidelines strongly recommend encouraging smokers to use NRT in a quit attempt demonstrates that NRT is safe in the overwhelming majority of the population.[23] When examining the safety of NRT, policymakers should be cognizant of the significant, pernicious and persistent adverse health consequences associated with smoking. In virtually all conditions, use of NRT is vastly safer than smoking.[24] Indeed, even with only moderate quit rates, the low cost of use and the tremendous benefits to health for each successful quitter make NRT one of the most cost-effective life-preserving interventions available to medical science.[25]

As safe and effective medications to treat tobacco dependence, NRT ought to be used far more frequently by the tens of millions of smokers desirous of quitting. Yet many smokers do not use NRT in a quit attempt, others use it at rates and dosages lower than recommended and still others opt not to attempt a quit despite the presence of NRT on the market. There is evidence that smokers are interested in using NRT with a quit attempt as typically the volume of calls to a Quitline increases significantly when free NRT is offered. What are the barriers preventing smokers from using NRT, from using NRT effectively or from attempting to quit? Petitioners identify some of the barriers and request general and particular action from the FDA. First, the FDA must adopt a framework within which NRT will be regulated—that framework must consider the significant public health impact and economic toll of smoking. Specifically, the FDA should modify packaging, labeling and other restrictions on NRT as defined in the Action Requested and explained more fully herein.

1. Combination Use of NRT is Safe and Effective: The FDA Should Amend Labeling Requirements to Reflect the Possibility of Combined Use of Certain Products

The efficacy of NRT is actually enhanced when used in ways that are somewhat inconsistent with current labeling. First, for many smokers, NRT is most effective when used in combination,

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[22] CPG at 42 (Strategy A4 Assist) and 44 (Table 3.2: Clinical guidelines for prescribing medication for treating tobacco use and dependence "All smokers trying to quit should be offered medication, except when contraindicated or for specific populations for which there is insufficient evidence of effectiveness .").

[23] *See* Ossip, *et al., Adverse effects with the use of nicotine replacement therapy among quitline clients*, 11 NICOTINE AND TOBACCO RESEARCH, 408-17 (2009)(quitline users who employed NRT in a quit attempt experienced adverse effects as expected by drug trials; effects were mild and rarely led to discontinuance of NRT use).

[24] Royal College of Physicians, HARM REDUCTION IN NICOTINE ADDICTION at 136 (October 2007)(hereafter RCP)("In any circumstance, the use of NRT is many orders of magnitude safer than smoking.").

[25] National Institute for Clinical Excellence (NICE), NICE Technology Appraisal Guidance No. 38: Nicotine Replacement Therapy (NRT) and Bupropion for Smoking Cessation, London, England (2002)(available at http://www.nice.org.uk/guidance/index.jsp?action=article&r=true&o=32347); *see also* Barriers Report at 6.

meaning more than one NRT product can be used by the quitting smoker at the same time. While almost all smokers seeking to quit benefit from the combination of NRT and counseling,[26] recalcitrant and heavy smokers in particular benefit from using a combination of NRT products in a manner inconsistent with the mandatory product labeling for approved NRT.[27] For example, those struggling with cessation while using the patch may find relief from an urgent craving by chewing a piece of nicotine gum or using another form of short-acting NRT. With the scientific base established, the PHS concludes that combination use of NRT "increases abstinence rates"[28] and that "NRT combinations are especially helpful for highly dependent smokers or those with a history of severe withdrawal."[29]

Yet required labeling warns against combination use:

Commit Lozenges and Nicorette Gum:
"Do not use if you . . . use a nicotine patch or other nicotine containing products."

Nicoderm CQ Patch:
"Do not use if you . . . use nicotine gum or other nicotine containing products."

Consumers have succeeded in quitting smoking by using NRT in various combinations and the PHS recommends such use, particularly for highly dependent smokers and those with a history of severe nicotine withdrawal symptoms. But because required labeling does not permit this combination use—indeed, warns against it—smokers do not know of the possibility and are discouraged from experimenting with combinations, manufacturers are prohibited from suggesting such use in labeling and marketing and physicians are likely unaware of the safety and efficacy of combined use or may be hesitant to recommend such off-label use for fear of liability. In addition, state health departments operating Tobacco Quit Lines, health plans, and employers can be hesitant to agree to combined NRT

[26] CPG at 101-02.

[27] CPG at 107; C. Sweeny, *et al*., *Combination nicotine replacement therapy for smoking cessation: rationale, efficacy and tolerability*, 15 CNS DRUGS 453(2001); K. Fagerstrom, *Combined use of nicotine replacement products*, 18 HEALTH VALUES 15 (1994); Stead (Cochrane).

[28] CPG Table 3.3 at 46.

[29] CPG Table 3.3 at 45; *see also* Piper, *et al*., *A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies*, 66 ARCH. GEN. PSYCHIATRY 1253 (November 2009)(patch plus lozenge resulted in higher quite rates than either product alone); L. Kozlowski, *et al*., *Advice on using over-the-counter nicotine replacement therapy—patch, gum, or lozenge--to quit smoking*, 32 ADDICTIVE BEHAVIORS 2140-50 (October 2007)(When using the patch, "[y]ou may need to add nicotine gum or lozenges to help get over the hump or you may need to use more than one patch at a time."); C. Sweeney, *et al*., *Combination nicotine replacement therapy for smoking cessation: rationale, efficacy and tolerability*, 15 CNS DRUGS 453-67 (2001); K. Fagerstrom, *Combined use of nicotine replacement products*, 18 HEALTH VALUES 15-20 (1994).

treatment protocols because of the current restrictive FDA labeling. The reality is that the risk of harm from overuse is quite low. Smokers who use NRT often underdose, using fewer lozenges or pieces of gum than directed on the label. The risk of a consumer experiencing nicotine toxicity while using NRT is quite low as smokers are keenly aware of their reaction to nicotine, having likely smoked for many years. Perhaps the overstated concern about too much NRT deters consumers from using a sufficient amount of NRT.

A barrier to combined use is the required labeling; hence, the FDA should modify the required labeling of NRT to allow for certain combinations. At the bare minimum, the FDA should remove the warnings against such use, making consumer experimentation and physician recommendation more likely. Optimally, the FDA should expressly state on package labeling that combined NRT (patch plus a short-acting form of NRT) has been demonstrated to reduce craving and increase quit rates.

2. NRT May Be Used Safely and Effectively Despite Occasional Cigarette Smoking: The FDA Should Amend NRT Labeling Requirements to Eliminate the Warning Against Modest Smoking While Using NRT

NRT may be used safely and effectively with continued use of cigarettes during a cessation attempt. For some smokers, the mere thought of an abrupt quit with a switch to NRT is sufficient to deter a quit attempt. While quitting abruptly, or "cold turkey," may be successful for some smokers, incremental reduction in smoking is sometimes the first step in successful smoking cessation. Yet as a smoker reduces cigarette consumption, she may suffer from nicotine withdrawal symptoms; those symptoms may be treated safely and effectively with NRT. Research shows that the use of NRT during incremental reduction in smoking is related to increased likelihood of long-term abstinence. A meta-analysis of four studies concluded that "pre-cessation patch treatment was found to produce a robust increase in quit rates compared to current regimens starting patch at quit day. Pre-cessation patch use represents a promising innovation in smoking cessation therapy with potential beneficial implications for improved public health by further increasing quitting success." [30] The studies did not report any serious negative health consequences from using NRT while smoking.[31] The PHS acknowledges this dynamic in the Guideline, citing favorably to studies that support the combined use of cigarettes and

[30] M. Schuurmans, *et al*., *Effect of pre-treatment with nicotine patch on withdrawal symptoms and abstinence rates in smokers subsequently quitting with the nicotine patch: a randomized trial*, 99 ADDICTION 634 (2004); J. Rose, *et al*., *Precessation treatment with nicotine skin patch facilitates smoking cessation*, 8 NICOTINE & TOBACCO RESEARCH 89 (2006).; C. Bullen, et al., *Pre-quitting nicotine replacement therapy: findings from a pilot study*, 3 TOBACCO INDUCED DISEASES 36 (2006); D. Wang, *et al.*, *"Cut down to quit" with nicotine replacement therapies in smoking cessation: a systemic review of effectiveness and economic analysis*, 12 HEALTH TECH. ASSESS. 1 (February 2008).

[31] CPG at 122 ("If this strategy is used clinically, patients should be advised to cease NRT use if they develop symptoms of nicotine toxicity (e.g., nausea, vomiting, dizziness).").

NRT during the early quit phase, but the agency does not include a recommendation on the issue, noting that "[t]he use of NRT while smoking contradicts NRT package inserts."[32]

Currently, under the red-lettered "Warnings" section, NRT labels caution : "Do not use if you continue to smoke . . . ."[33] On patch products, the warning is even harsher: "When using this product, do not smoke even when not wearing the patch. The nicotine in your skin will still be entering your blood stream for several hours after you take off the patch."[34] Directions on the gum and lozenge advise users to "stop smoking completely before using" the lozenge or gum. Together these warnings and directions likely discourage some would-be quitters from trying a quit attempt that employs smoking reduction with use of NRT. The warnings may wrongly discourage those trying to quit from attempting a reduce-to-quit approach and make it highly unlikely that a physician would recommend, suggest or approve of such an approach. The frequent consequence of this labeling is that when the person smokes a relapse cigarette, he believes that he must cease using the NRT or else something dangerous will happen. Such fears are unfounded and the labeling should be amended accordingly.

These warnings may also eliminate the possibility of using NRT to treat the symptoms of temporary abstinence; for example, chewing nicotine gum while at work or on an airplane.[35] Legislation prohibiting smoking in public places and workplaces has been passed in many jurisdictions across the country; air and mass transit have been smokefree for many years. The creation of smokefree environments encourages some smokers to quit; indeed, that is one public health benefit of such legislation.[36] For smokers unwilling or unable to quit, however, smokefree environments create difficult situations as suffering from nicotine withdrawal interferes with productivity at work and enjoyment of public venues. Allowing the use of NRT for temporary abstinence will assist these smokers by treating the symptoms of nicotine withdrawal and may result in a reduction in the number of cigarettes smoked.

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[32] CPG at 122.

[33] Required labeling for all OTC NRT.

[34] Required labeling for NRT patch products.

[35] This, too, creates a market imbalance with tobacco products as many smokeless tobacco products are marketed for use by smokers during times that smoking is prohibited, such as at the office or on at a concert. If unregulated smokeless tobacco products—that cause cancer and other ailments-- may be marketed in this manner, there is no justification for the stern warnings against such use of NRT, approved as safe medicines. Indeed, some smokers not planning to quit but nevertheless enticed to try NRT are persuaded to attempt quitting after use of the NRT. The side benefit of not precluding use of NRT in such circumstances may be smoking reduction.

[36] *The Health Consequences of Involuntary Exposure to Tobacco Smoke,* A Report of the Surgeon General (2006)(hereafter SGR 2006); National Cancer Institute, *Population Based Smoking Cessation: Proceedings of a Conference on What Works to Influence Cessation in the General Population*, Smoking and Tobacco Control Monograph No. 12, NIH Pub. No. 00-4892, November 2000. *See also*, *Factsheet: Smokefree Laws Encourage Smokers to Quit and Discourage Youth From Starting*, Campaign for Tobacco Free Kids (July 27, 2006).

If a smoker who works in a smokefree environment uses NRT during the work hours, she may smoke fewer cigarettes as a result of the 8-hour weekday abstinence. The same dynamic may apply to temporary abstinence due to other smokefree environments. And, ultimately, this use may lead to a successful quit attempt. [37] Indeed, use of NRT for temporary abstinence may work to increase smokers' awareness that it is the nicotine, not the cigarettes, to which they are addicted, making a quit attempt with NRT more likely. Package labeling and clinician recommendations should not discourage such use for those unwilling or unable to quit smoking.

An agency committed to improving public health should not effectively shut off a possibly effective method for smokers to achieve smoking cessation or reduce cigarette consumption. Because the step down approach to smoking cessation is palatable and effective for some smokers, concomitant use of NRT and cigarettes should not be discouraged in NRT package labeling.[38] Clinicians should consider offering this combination to heavy smokers, those with anxiety over abrupt smoking cessation, and those who have experienced severe nicotine withdrawal symptoms. Moreover, consumers should not be discouraged from using NRT to treat the symptoms of temporary abstinence.

3. NRT May be Used Safely and Effectively Beyond the Recommended 10 to 12 Week Cycle: Package Labeling Should Reflect this Safe and Effective Use of NRT

Long-term use of NRT, though contrary to current labeling, is a safe and effective way to sustain smoking cessation. Most NRT provides for a 10 to 12 week course of treatment; after that period, the smoker should be nicotine-free and stop using NRT.[39] Moreover, the implication in this 12-weeks-and-done warning is that there are sufficient negative health consequences to using NRT to stop after that period of time; that is simply wrong. As is, the labels imply that these smokers have failed to quit successfully or they must continue the quit attempt without the assistance of NRT if they still crave nicotine after 12 weeks of NRT use. That is a wrong and dangerous message to send, especially to a

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[37] At least one study has noted the possibility that unwilling quitters be offered NRT as a means to reduce the number of cigarettes smoked daily. The study showed that although expressing no desire or interest in quitting, some smokers who adopted the reduction approach ultimately quit smoking. Yet the results were not strong enough to suggest such an approach be recommended; rather, further study was suggested. *See* L. Stead, *et al.*, *Interventions to reduce harm from continued tobacco use*, COCHRANE DATABASE OF SYSTEMATIC REVIEW (2007). Encouraged by this possibility, the PHS likewise recommends further research in this area. CPG at 124.

[38] Over half of current U.S. smokers have tried to reduce cigarette consumption and around a quarter are planning to do so in the next year. Shiffman, *et al.*, *Smokers' interest in using nicotine replacement to aid smoking reduction*. 9 NICOTINE TOB RES. 1177-82 (November 2007). In addition, placebo-controlled trials of NRT to aid smoking reduction have found that NRT used in this way results in more quitting as well as greater smoking reduction (as compared to placebo). Wang, *et al*., *'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis*, 12 HEALTH TECHNOL ASSESS. iii-iv, ix-xi, 1-135 (February 2008).

[39] Nicorette: "Use Nicorette for the full 12 weeks."; Commit: "Use Commit for the full 12 weeks."; Nicoderm CQ: "[S]top using the patch after 10 weeks."

consumer who had remained smokefree with NRT for 12 weeks. That is a tremendous accomplishment for a smoker.

Studies show that for some smokers, long-term use of NRT supports continued abstinence. Nearly one-third of Lung Health Study participants who remained cigarette-free after 2 months continued to use nicotine gum safely; some continued use for up to five years.[40] According to the PHS, "[r]esults of the inclusive meta-analysis indicated that long-term patch and gum are effective. Evidence indicates that long-term use of gum may be more effective than a shorter course of gum therapy."[41] The PHS adopts the appropriate reference when concluding: "[C]ontinued use of such medication clearly is preferable to a return to smoking with respect to health consequences."[42] Long-term use of NRT is an effective approach to life-long cessation and smokers and doctors should understand that, while living nicotine-free is preferred, long-term use of NRT is safe and effective and far superior to smoking.[43]

Because use of NRT beyond the recommended 10 to 12 weeks is safe and effective, the FDA should modify required labeling. Consumers should not be discouraged from using NRT beyond the recommended timeframe and doctors should be encouraged to suggest such use when appropriate.

4. Harsh Warnings Wrongly Discourage Those with Heart Disease and Other Conditions from Using NRT: The FDA Should Modify Label Requirements to Prevent Such Discouragement

Product warnings communicate concerns about use of the NRT by consumers with heart disease, recommending that a smoker with heart disease consult a physician before using NRT. This is also true for smokers on a sodium-restricted diet or those with high blood pressure not controlled by

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[40] M. Nides, *et al*., *Predictors of initial smoking cessation and relapse through the first 2 years of the Lung Health Study*, 63 J. CONSULT. CLINIC. PSYCHOL. 60 (1995); R. Murray, *et al*., *Safety of nicotine polacrilex gum used by 3,094 participants in Lung Health Study Research Group*, 109 CHEST 438 (1996); J. Hughes, *et al*., *Effect of cost on the self-administration of nicotine gum: a preliminary study*, 20 PREV. MED. 486 (1991); J. Henningfield, *et al*., *Nicotine medications for smoking cessation*, 333 N.ENG.J.MED. 1196 (1995).

[41] CPG at 126.

[42] CPG at 126. "This is because, unlike smoking, these medications do not (a) contain non-nicotine toxic substances (e.g. 'tar,' carbon monoxide, formaldehyde, benzene); (b) produce sharp surges in blood nicotine levels; and/or (c) produce strong dependence." *Id. See also* Royal College of Physicians, HARM REDUCTION IN NICOTINE ADDICTION at 136 (October 2007)("Evidence on the safety of long-term use of NRT is lacking, but there are no grounds to suspect appreciable long-term adverse effects on health.").

[43] *See* L. Kozlowski, *et al*., *Advice on using over-the-counter nicotine replacement therapy—patch, gum, or lozenge--to quit smoking*, 32 ADDICTIVE BEHAVIORS 2140-50 (October 2007)("If you find NRT helpful and you need to use it for a long time to stay off cigarettes, do not be disappointed or worried—be proud of yourself because you have stopped smoking.")

medication.[44] This recommendation may deter smokers with heart disease or other conditions from attempting to quit or from using NRT in a quit attempt. Smokers may read the overstated warning about visiting a doctor if the smoker has heart disease and discard the NRT, either because the smoker has heart disease and is fearful of a product that might increase risk of acute harm or because the smoker does not have heart disease but is fearful of using a product that may impose negative cardiac consequences. There is evidence to the contrary; use of NRT is not associated with acute cardiac events. Hence, this warning is not only unnecessary but harmful to effectiveness of NRT. Smokers with heart disease are among those for whom smoking cessation is an imperative to improving health as smoking not only creates and exacerbates heart disease, smoking or exposure to secondhand smoke can cause cardiac arrest and death in those with heart disease. [45]

Smokers with heart disease should be strongly encouraged to quit and to use effective NRT in doing so because there is no increased risk of heart disease or acute cardiovascular outcomes associated with use of NRT. The PHS makes clear that the link between use of NRT and cardiovascular risk has "been studied systematically" and studies "have documented the lack of an association between the nicotine patch and acute cardiovascular events, even in patients who continued to smoke while on the nicotine patch."[46] The PHS conclusion is mirrored by the Royal College of Physicians: "[T]he clinical trial and observational data indicate that, in relation to cardiovascular outcomes, NRT is safe and specifically does not increase the incidence of acute cardiovascular events or of sudden death in healthy volunteers, the general population or patients with pre-existing cardiovascular disease."[47] That consumers have picked up on the media hype is reflected in consumer perception: 35% of smokers believe that use of NRT presents a higher risk of heart attack than smoking.[48] Package labeling should reflect the actual risk, not perceived or exaggerated media-hyped risk.

The FDA should adopt product labeling that encourages, rather than discourages, smokers with heart disease to attempt to quit using NRT. There is no debate that NRT may be used safely in this population for whom smoking is particularly dangerous. Therefore, the label requirement indicating that those with heart disease should seek medical advice prior to using NRT should be eliminated.

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[44] Given that the Dietary Guidelines of the USDA recommend that all Americans eat a diet "low in salt (sodium)," it is entirely possible that this exaggerated warning interferes with smokers' quit attempts by imposing a doctor's visit before "safe" use of the NRT. *See* Dietary Guidelines for Americans, United States Department of Agriculture (2005)(available at http://mypyramid.gov/guidelines/index.html).

[45] SGR 2006 (Chapter 8).

[46] CPG at 127 (citing 7 supportive studies).

[47] Royal College of Physicians, HARM REDUCTION IN NICOTINE ADDICTION at 123, 246 (October 2007).

[48] M. Bansal, *et al*., *Stop-smoking medications: Who uses them, who misuses them, and who is misinformed about them*, 3 NICOTINE & TOBACCO RESEARCH S303 (2004).

5. Packaging Standards and Sales Limitations Reduce the Accessibility and Use of NRT: The FDA Should Expand Allowable Pack Sizes and Retail Locations for NRT

That the FDA limits the availability of NRT to certain establishments and certain pack sizes likewise contributes to less effective use of NRT. Consumers should have access to NRT products in a one-day supply. For consumers who have at best moderate confidence that NRT will assist in quitting, spending a significant amount of money for a first quit attempt with NRT is an unattractive option. Indeed, for some consumers the price is a complete deterrent to NRT use; this is particularly true for consumers in states with low cigarette taxes.[49] Further, one study concludes that "sample size" NRT packages should be available because a consumer who is able to experiment with various forms of NRT is more likely to choose the method most appropriate and effective for her.[50] As one consumer specialist puts it: "Let them kick the tires, test a service/product before buying into it. Lower the bar, make initial quit attempt less costly, psychologically and financially."[51] An interested but anxious smoker may be willing to purchase a one-day supply of nicotine gum for less than $10 in a bid of faith in himself and as encouragement to quit but he may not be willing to part with more significant funds for a week's supply if he is less than 100% confident in himself or the product.

Moreover, a small pack size will allow for temporary abstinence in circumstances that benefit the smoker and those in her presence—and may lead to a desire or interest in cessation if the NRT shows promise. For example, a grandmother who smokes may be planning to visit her young grandchildren for the day in the children's smokefree home. If that smoker is able to purchase a one-day supply of NRT to get her through the visit without the need for smoking,she will have avoided the physical and emotional toll of nicotine withdrawal, enjoying every minute with her grandchildren. The grandmother will have avoided exposing the children to secondhand smoke and prevented the grandchildren from seeing their grandmother, an adult who they respect, engage in the high-risk behavior of smoking. That is reason enough to offer the one-day pack. Further, a smoker who is able to access a one-day pack of NRT, with no intention of quitting, may ultimately engage in a quit attempt as a result of exposure to the NRT. Therefore, ready availability of small packages for temporary cessation may ultimately contribute to increased, permanent cessation. In addition, there are a number of

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[49] *Cf.* J. Taurus, *et al*., *The impact of advertising on nicotine replacement therapy demand*, 60 SOC. SCI. MED.2351 (May 2005)(decreases in price of NRT and increases in price of cigarettes leads to measurable increase in demand for NRT); K. Metzger, *et al*., *Use of pharmacy data to evaluate smoking regulation's impact on sales of nicotine replacement therapies in New York City*, 95 AM. J. PUBLIC HEALTH 1050 (June 2005)(NRT sales increased after effective date of smokefree public places law and tobacco tax increases.).

[50] N. Schneider, *et al*., *Preferences among five nicotine treatments based on information versus sampling*, 10 NICOTINE AND TOBACCO RESEARCH 179 (January 2008).

[51] C. Di Clemente and T. Orleans, *Designing for Demand: Views from the Consumer Demand Roundtable*, Society for Research on Nicotine and Tobacco (SRNT) Preconference Symposium, "Increasing Access to Effective Treatments: The Case for More Flexible Regulatory Policy; Austin, TX (February 21, 2007)(attributed to Peter Coughlan, PhD, President, IDEO).

occupations in which experiencing acute nicotine withdrawal may be dangerous (i.e., neurosurgeon, air traffic controller, long-distance pilot) and situations in which the same is true (i.e., mother driving long distance in car with children). Therefore it makes sense to allow individuals to use NRT to treat nicotine withdrawal as a primary indication in situations in which the smoker is not permitted or chooses not to smoke.

To some extent, reducing pack size will result in NRT being available in more retail locations. Certainly some establishments that could carry NRT because they do carry other OTC drugs do not offer NRT because of the price of the product. Convenience stores that sell single dose packages of aspirin, acetaminophen or anti-acids are unlikely to carry an expensive pack of NRT because consumers do not anticipate spending that amount of money in a convenience store and higher price items invite crime in some locations. Moreover, limited shelf space makes a bulky 2-week pack of patches unattractive to a retailer whereas smaller packages that sell for much smaller prices may be worth the shelf space. A single day supply of NRT for under $10 may be a product worth stocking. As these stores likely carry the product whose devastation NRT is designed to ameliorate and with whom NRT competes—cigarettes—giving consumers the option of NRT in place of a pack of cigarettes can only lead to increased use of NRT and perhaps increased cessation. The mere presence of NRT in establishments that sell cigarettes and other tobacco products may boost cessation attempts as consumers seeing the NRT while purchasing the tobacco product may subconsciously reconsider at time of purchase or some time thereafter.

It bears mentioning that making NRT more widely available by allowing for smaller pack sizes with lower prices responds to the demographics of smokers. Smoking prevalence is highest among those at lower income levels.[52] Those who earn a daily wage and who may purchase a pack of cigarettes when the cash is available simply cannot purchase an expensive box of nicotine patches to start a quit attempt. Quitting is hard for every smoker but the financial barrier to access most acutely impacts those who are most likely to be smoking and without access to medical resources to help a smoker quit.

There is no risk associated with small pack size and there is benefit to gain from small pack availability. The FDA ought to consider the positive effect of small pack sizes and relax packaging restrictions.

6. Concerns about Developing an Addiction to NRT are Negligible

Studies show that few consumers continue their nicotine dependence created by smoking by switching to dependence on OTC NRT—the gum, lozenge or patch. These are slow-acting nicotine delivery devices that do not create the same immediate satisfaction that inhaling nicotine through a cigarette might create. Therefore, although dependence can occur, it is not typical and is rare with the

[52] Centers for Disease Control, *Cigarette Smoking Among Adults, 2007*, MMWR, 57:1221-1248 (November 14, 2008). In fact, low-income smokers are less likely to quit smoking as a result of cigarette price increases. Frank, *et al*., *Cigarette Prices, Smoking and the Poor: Implications of Recent Trends*, 97 AM. J. PUBLIC HEALTH 1873 (October 2007). Lack of access to medical resources, including NRT, likely contributes to this unfortunate dynamic.

nicotine patch.[53] Faster delivery devices, such as nasal spray, may be in use for longer than initially recommended by a minority of users. Moreover, each NRT product "delivers smaller doses at slower rates than smoked tobacco, and so they are correspondingly less addictive than cigarettes."[54] Continued use of NRT is much less harmful to health than continued dependence on and use of cigarettes.

7. Other Issues for Consideration: Use of NRT by Adolescents and Pregnant Women

Petitioners are not seeking specific changes to FDA policy related to the use of NRT in adolescents. In the absence of solid evidence showing that OTC NRT is effective for youth, and given that Petitioners are seeking some broadening of access to these products, we support measures, including labeling, designed to ensure that these products are not sold to minors. We note, however, that NRT, although of limited efficacy, is safe for use in young smokers.[55] Similarly, Petitioners seek no changes specifically related to FDA policy as it relates to use of NRT by pregnant women.[56] Product labeling warns pregnant women that NRT should be used only on the advice of a medical professional and that the risks of NRT on fetus health are not fully known. Interestingly, though, the product labeling does warn that "[s]moking can seriously harm your child" and that "[t]his medicine is believed to be safer than smoking."[57] This is precisely the perspective sought by Petitioners; that the risks of use of NRT be weighed against the risks of smoking for all smokers and that product labeling reflect that paradigm for all smokers, not just pregnant women.

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[53] R. West, *et al*., *A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler*, 149 PSYCHOPHARMACOLOGY (Berl) at 198-202 (April 2000); J. Hughes, *et al.*, *Dependence on and abuse of nicotine replacement medications: An update.* In: Benowitz NL, editor. Nicotine safety and toxicity. New York: Oxford University Press; 1998 at 147-57.

[54] Barriers Report at 6 and 12.

[55] CPG at 161.

[56] To the extent that drug manufacturers submit it, the FDA should consider fully evidence that NRT use in pregnancy does not pose risk of harm to the fetus or the mother. The negative impact of maternal smoking during pregnancy is significant. Emerging research indicates the possibility of fetal benefits from the mother's use of nicotine replacement therapy even if the mother does not ultimately quit smoking. *See* C. Oncken, *et al., Nicotine gum for pregnant smokers: a randomized controlled trial*, 112 OBSTET. GYNECOL. 859 (October 2008)("Although nicotine gum did not increase quit rates, use of nicotine gum increased birth weight and gestational age, two key parameters in predicting neonatal health."); *see also* K. Strandberg-Larsen, *et al*., *Use of nicotine replacement therapy during pregnancy and stillbirth: a cohort study*, 115 BJOG 1405 (October 2008)(no indication of increased risk of stillbirth from use of NRT during pregnancy); K. Pollak, *et al*., *Nicotine replacement and behavioral therapy for smoking cessation in pregnancy*, 33 AM. J. PREV. MED. 297 (October 2007); *see also* RCP at 125 ("[T]he available data on the safety of NRT during pregnancy are limited . . . . However, the data available suggest that nicotine does not reduce birth weight, and is not a cause of serious developmental abnormalities."). If pregnant women use NRT to stop smoking, at least during pregnancy, the result will likely be healthier mothers *and* healthier children.

[57] Commit, Nicorette, Nicoderm CQ.

C. CONSUMER AND CLINICIAN PERCEPTION ABOUT NRT IS FLAWED: CHANGES IN PACKAGE LABELING MAY IMPROVE SMOKER AND CLINICIAN UNDERSTANDING OF THE SAFETY AND EFFICACY OF NRT USE

In clinical trials, NRT is quite effective in assisting smokers with cessation. While NRT is also effective in over-the-counter, non-clinical use, certain factors interfere with NRT being used in the first instance and in being used as effectively as possible. Consumer and clinician misperception about the safety and efficacy of NRT prevent full and effective use of NRT. Many of these hurdles and misperceptions are created or enhanced by current FDA practices with respect to the sale, marketing, and packaging and labeling of NRT. That is why Petitioners are seeking changes to labeling and packaging restrictions imposed by the FDA.

1. Smokers Believe NRT is Dangerous, Inhibiting Comprehensive Use of NRT

Consumers have long believed that nicotine is the harmful agent in cigarettes, meaning they believe that nicotine causes heart disease, cancer, respiratory ailments, and other tobacco-caused illnesses. This fuels the misperception many consumers hold about the safety of NRT.[58] The most persistent and pernicious belief among smokers that interferes with their interest in using NRT is the belief that heart attack risk is greater or the same for NRT use as for cigarette use.[59] One study revealed that 35% of smokers believed NRT to be "more likely" or "about the same" with respect to the risk for heart attack.[60] Add those who "don't know" and the total is 65%; only 35% of smokers believed the risk of heart attack to be less for smoking than for NRT use.[61] A recent study found that this misperception endures: 66% of smokers or ex-smokers agreed somewhat with the statement that "stop-smoking products with nicotine are just as harmful as cigarettes."[62] To be sure, early media reports based on speculation and anecdote fostered these misperceptions, but the manner in which FDA has chosen to regulate these products, including the mandatory labeling on NRT, perpetuates this myth. Sadly, many

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[58] *See generally* Barriers Report at 8-9.

[59] M. Bansal, *et al*., *Stop-smoking medications: Who uses them, who misuses them, and who is misinformed about them*, 3 NICOTINE & TOBACCO RESEARCH S303 (2004). Smokers also are skeptical that NRT will work and yet vastly overestimate their likelihood of quitting successfully. *Id.* This makes smokers less likely to initiate NRT use and to be more pessimistic about its efficacy if used during an unsuccessful quit attempt. Both of these factors curtail full effectiveness of NRT in the population.

[60] M. Bansal, *et al*., *Stop-smoking medications: Who uses them, who misuses them, and who is misinformed about them*, 3 NICOTINE & TOBACCO RESEARCH S303 (2004).

[61] *Id.*

[62] S. Shiffman, *Underutilization of evidence-based medications and misperceptions of NRT safety*, Society for Research on Nicotine and Tobacco (SRNT) Preconference Symposium, "Increasing Access to Effective Treatments: The Case for More Flexible Regulatory Policy; Austin, TX (February 21, 2007)(available at http://roswelldocs.com/srnt.htm).

smokers being assessed for treatment frequently point to the wording on the labeling of NRT as indicators that the effective and safe cessation aids may be dangerous.

In addition, consumers underestimate the efficacy of NRT and may confound this belief by underutilizing NRT. For example, although gum labeling directs consumers to use about 9 pieces of gum daily, one study revealed that on average smokers trying to quit used only 4.1 pieces of gum a day. [63] Whereas labeling suggests use for 10-12 weeks, many smokers used NRT for less than 5 weeks, reducing the likelihood of a successful quit attempt with NRT and fueling the perception of lack of efficacy.[64] And the lack of counseling from medical professionals means that the product label, with its overstated warnings, serves as the consumers' only source of information about NRT.

Labeling should also be in plain language that can be understood by those without significant education beyond primary school. Smoking prevalence is highest among adults who have not graduated from high school and lowest among those with an undergraduate or graduate degree.[65] To reach the most significant portion of the smoking population, package labeling must be written in an accessible manner to those with moderate reading skills.

Because consumers rely on package labeling and may act cautiously in response to current required language, amending labeling may increase the use of NRT and improve users' compliance with directions on use, thereby increasing successful quit attempts.

2. Clinician Misunderstanding about NRT Prevents Effective Counseling on Use of NRT

The impact of NRT labeling is heightened by the low rate at which clinicians provide counseling to patients on the use of NRT to quit smoking. One study revealed that less than one in four smokers were offered tobacco counseling at a physician visit and a mere 2.4 percent of doctor visits by smokers resulted in a prescription for smoking cessation. [66] Too often clinicians ignore the Clinical Practice Guidelines , the resource that strongly encourages clinicians to offer cessation assistance and to recommend use of NRT to all smokers at every visit.[67] Smoking will continue to be the most persistent

[63] S. Shiffman, *Underutilization of evidence-based medications and misperceptions of NRT safety*, Society for Research on Nicotine and Tobacco (SRNT) Preconference Symposium, "Increasing Access to Effective Treatments: The Case for More Flexible Regulatory Policy; Austin, TX (February 21, 2007)(available at http://roswelldocs.com/srnt.htm).

[64] S. Shiffman, *et al*., *Persistent use of nicotine replacement therapy: an analysis of actual purchase patterns in a population based sample*, 12 TOBACCO CONTROL 310-316 (September 2003).

[65] Centers for Disease Control, *Cigarette Smoking Among Adults, 2007*, MMWR, 57:1221-1248 (November 14, 2008).

[66] M. Steinberg, *et al*., *Gender and age disparities for smoking cessation treatment*, 30 AM. J. PREV. MED. 405 (2006).

[67] D. Longo, *et al*., *Characteristics of smoking cessation guideline use by primary care physicians*, 103 MO. MED. 180 (March/April 2006); M. Ward, *et al*., *Physician knowledge, attitudes and practices regarding a widely implemented*

preventable cause of illness and death in this country if medical professionals continue to fail their patients who smoke. Why does such a chasm between best practices and real world medical practice exist?

Unfortunately, some health professionals believe that nicotine causes cancer and that if a patient is properly motivated to quit smoking, NRT is unnecessary.[68] These and other factors[69] contribute to the low rate at which clinicians encourage smokers to use NRT. [70] Without effective advice and direction from a medical professional, a smoker must rely on NRT packaging and labeling to assess effectiveness and safety.[71] When doing so, smokers read a litany of exaggerated concerns that create the impression that the NRT product presents significant risk to the user. Moreover, the packaging does not remind smokers of the profound negative health consequences of smoking, risks the smoker should be weighing when deciding whether to use the NRT.[72]

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guideline, 8 J. EVAL. CLIN. PRACT.155 (May 2002). The problem persists across health professionals. *See, e.g.,* A. Ward, *et al*., *Addressing tobacco in managed care: a survey of dentists' knowledge, attitudes and behaviors*, 92 AM. J. PUBLIC HEALTH 997 (June 2002); J. Price, *et al*., *Perceptions and use of smoking cessation in nurse-midwives' practice*, 51 J. MIDWIFERY WOMEN'S HEALTH 208 (May 2006).

[68] L. Kozlowski and K. Dollar, *Two issues with health care professionals' views of NRT: Misperceived risks and moral disapproval*, Society for Research on Nicotine and Tobacco (SRNT) Preconference Symposium, "Increasing Access to Effective Treatments: The Case for More Flexible Regulatory Policy; Austin, TX (February 21, 2007)(small study of 30 doctors in 11 states found 25% believe nicotine causes cancer and 10% unsure of that)(available at http://roswelldocs.com/srnt.htm). The CPG was widely disseminated to clinicians free of charge and is readily available online.

[69] Doctors cite various reasons for failing to treat smokers according to best practices, including that such discussions are too time-consuming, ineffective, and unpleasant; many doctors reported lack of confidence in being able to properly handle such a conversation or general lack of knowledge in the area. Stunningly, 5 percent of doctors believed such a discussion to be outside the boundaries of their professional responsibilities. F. Vogt, *et al*., *General practitioners' and family physicians' negative beliefs and attitudes toward discussing smoking cessation with patients: a systematic review*, 100 ADDICTION 1423 (2005).

[70] *See* A. Thorndike, *et al*., The *treatment of smoking by US physicians during ambulatory visits: 1994*, 97 AM. L. PUBLIC Health 1878 (October 2007); T. Marcy, *et al*., *Facilitating adherence to the tobacco use treatment guideline with computer-mediated decision support systems: physician and clinic office manager perspectives*, 41 PREV. MED. 479 (August 2005)

[71] Even when doctors prescribe NRT, they do an inadequate job with patient preparation and counseling. *See* S. Shiffman, *et al*., *Physicians' counseling of patients when prescribing nicotine replacement therapy*, 32 ADDICT. BEHAV. 728 (April 2007)(of 993 smokers who filled an NRT prescription: 18% had not met with physician; 33% received no instruction on use; 50% were not told about potential side effects).

[72] Pregnant women are informed that smoking may harm the child and encouraged to quit smoking without use of NRT. Because this warning focuses on the child in utero and calls out only to pregnant women, it does not function as a general reminder that smoking is quite harmful to health.

To the extent that product labeling will enhance physician understanding of the very minimal health risks associated with use of NRT, the FDA should take steps to improve required labeling on NRT.

CONCLUSION

Smoking is the leading cause of preventable death in the United States; every agency that is involved in addressing this crisis must take bold and aggressive action to reduce smoking prevalence. The FDA can contribute to reduction in smoking prevalence by swiftly approving medicines designed to assist in smoking cessation, allowing all approved NRT products to be sold over-the-counter, and issuing NRT product labeling that effectively explains the tremendous benefits of smoking cessation and realistically addresses the modest risks of using NRT. The FDA must adopt principles applicable to the approval and regulation of NRT that consider continued smoking as the comparator to NRT, provide for easy-to-understand and accurate instructions and warnings, and allow access to one-day supply packages.

SPECIFIC PROPOSAL FOR PACKAGE LABELING LANGUAGE

Set forth below is language that Petitioners suggest as a starting point for the FDA to use when crafting appropriate package labeling language for NRT products. There may be product-specific language that should be added to this proposal but this is overarching language for all NRT products. Petitioners urge the FDA to modify the language presented here to make the text as accessible as possible to all consumers. As indicated previously, smoking is most prevalent in populations with lower levels of education. Therefore, it is imperative that linguistic specialists review any package labeling to insure that the language is at the appropriate grade level.

Indications:

Use of [NRT type] reduces nicotine withdrawal symptoms (such as feeling tense and irritable). It reduces cravings for nicotine when you are not smoking and will help you to quit smoking. Use of [NRT type] will also have these effects when you are in a situation in which you cannot use tobacco for an extended period of time (e.g. a work-day at a smoke-free environment, or a long distance flight).

Warnings:

Talk to your doctor before you use [NRT type] if you are pregnant or breastfeeding. This medicine is safer than smoking (as tobacco smoke contains thousands of chemicals, including nicotine). Nicotine can harm your baby so this medicine should only be used if you are not able to quit smoking without it.

[Note: In this section, the FDA should remove the "Do Not Use" warning for when smoking, chewing smokeless tobacco, or using other products containing nicotine.]

Talk to your doctor:

[NRT type] can be used to quit smoking when you have heart disease. Tell your doctor that you intend to use [NRT type] if you:

- Had a heart attack in the past two weeks.
- Have an irregular heartbeat that limits how active you can be.
- Have chest pain (angina).
- Have an allergy to adhesive tape or have very sensitive skin. [patch only]
- Are less than 18 years of age. This medicine is not FDA approved for those less than 18 years of age.

Using two kinds of nicotine replacement medicines:

- [NRT type] can be used while using a different type of nicotine replacement medicine. Use of two types of nicotine replacement medicine may help you if you are a heavy smoker (smoke 20 or more cigarettes per day). If you are having nicotine craving when using only one type of nicotine replacement medicine, try using a second type of nicotine medicine.
- To use two types of nicotine medicine use the nicotine patch along with one of these other nicotine medicines:
    - nicotine gum
    - nicotine lozenge
    - nicotine nasal spray
    - nicotine inhaler

Using nicotine replacement medicines while smoking:

This medicine is intended to help you to quit smoking. You can start using it on the day you quit smoking, or you can use it while you reduce the number of cigarettes you smoke each day. If you are using the medicine to help cut down your smoking you should have a cut-down plan with a clear date when you will stop smoking.

If you experience craving for a smoke, then use the medicine, rather than smoking.

You may have side effects:

Most side effects are minor and will go away in a week or two. Ask your doctor if you should keep using [NRT type] if you have:

- Irregular heartbeat or palpitations (when your heart beats funny)
- Nausea or vomiting

Stop using the [NRT type] immediately if you have:

- **A serious rash on your body that does not go away**
- **Trouble breathing or if your throat swells**

[Note: The FDA should maintain the current labeling stating "Keep out of reach of children and pets."]

[The FDA should maintain the current Directions, with the following addition.]

- If you still have nicotine craving while using [NRT type} you may use another type of nicotine medicine at the same time. This may help you quit.
    - [if patch] Try using some nicotine gum, nicotine lozenges, nicotine inhaler, or nicotine nasal spray. Follow the directions on the package.

[If short-acting form of NRT] Try using a nicotine patch in addition to [NRT type].

Use enough of the medicine to reduce your cravings and withdrawal symptoms (e.g. feeling tense and irritable) to levels that you can mange comfortably without smoking.

ENVIRONMENTAL IMPACT

The action requested in this Petition will not have any significant effect on the quality of the human environment.

ECONOMIC IMPACT

No statement of economic impact of the requested action is presented as none has been requested by the Commissioner.[73]

CERTIFICATION

The undersigned certify, 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 and which are unfavorable to the petition.

Respectfully Submitted,

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Society for Research on Nicotine and Tobacco (SRNT)

[73] 21 C.F.R. 10.30(b).