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Re: Docket No. FDA-2008-P-0116
Docket No. FDA-2010-P-0089
Docket No. FDA-2010-P-0454

Dear Dr. Shah, Ms. Hoke and Mr. Myers:

This is a combined response to three citizen petitions asking the Food and Drug Administration (FDA or the Agency) to take various actions regarding the regulation of over-the-counter (OTC) nicotine replacement therapy (NRT) drug products.

The State of New York’s Commissioner of Health submitted a petition to the Agency dated January 22, 2008 (the NY Petition). The University of Maryland School of Law submitted a petition to the Agency on behalf of the Association for the Treatment of Tobacco Use and Dependence (ATTUD) and the Society for Research on Nicotine and Tobacco (SRNT) dated February 11, 2010 (the UMD Petition). \(^1\) A third petition, dated

\(^1\) We note that ATTUD and SRNT submitted comments to the NY Petition.
August 26, 2010, was submitted by four not-for-profit public health organizations: the American Cancer Society Cancer Action Network, the American Lung Association, the Campaign for Tobacco-Free Kids, and the American Legacy Foundation (the Public Health Group or PHG Petition). These three petitions raise many common issues.

For example, the Petitions request that we take the following actions:

- Modify current OTC NRT labeling to: (1) disclose the risks and benefits of OTC NRT relative to continued cigarette use,\(^2\) (2) allow for the use of OTC NRT products in situations of temporary abstinence from cigarettes,\(^3\) (3) allow for the use of OTC NRT products concomitantly with other NRTs\(^4\) and with cigarettes,\(^5\) and (4) allow for the use of OTC NRT products beyond the currently labeled treatment period (up to 12 weeks, depending on the product);\(^6\) and
- Evaluate the safety of OTC NRT by comparison to continued tobacco use rather than placebo.\(^7\)

The NY Petition and the UMD Petition both request that we take the following actions:

- Allow the sale of OTC NRT drug products in all retail locations where cigarettes are sold by removing restrictions governing what types of outlets can sell OTC NRT products;\(^8\)
- Allow OTC NRT drug products to be sold in “sample” or “daily” units (i.e., containing an amount of NRT that would typically be consumed in a 24-hour period) at affordable and competitive prices;\(^5\) and
- Modify labeling to indicate that OTC NRT is safe and safer than cigarettes for all smokers, including those with cardiovascular disease, those who are pregnant, and adolescents.\(^10\)

Finally, the PHG Petition requests that we take the following actions:\(^11\)

- Indicate our willingness to review data on whether OTC NRT products that deliver a higher dose or deliver doses at a different rate might be safe and effective for cessation;
- Initiate a program whereby the Agency will collaborate with manufacturers of smoking cessation products to identify appropriate trial designs;

\(^2\) NY Petition at 1; UMD Petition at 3, 18-21; PHG Petition at 6.
\(^3\) NY Petition at 2, 3; UMD Petition at 3, 11-12. This issue is not explicitly addressed in the PHG petition.
\(^4\) UMD Petition at 3, 9-10; PHG Petition at 8. This issue is not explicitly addressed in the NY Petition.
\(^5\) UMD Petition at 3, 10-12; PHG Petition at 6-7; NY Petition at 3.
\(^6\) NY Petition at 3; UMD Petition at 3, 12-14; PHG Petition at 7.
\(^7\) NY Petition at 2; UMD Petition at 3, 5, 21; PHG Petition at 1, 5-6.
\(^8\) NY Petition at 2; UMD Petition at 4, 15-17.
\(^9\) NY Petition at 2; UMD Petition at 3, 15-17.
\(^10\) NY Petition at 2, 3; UMD Petition at 8, 14-15, 17-18.
\(^11\) PHG Petition at 2, 7, 8-9.
• Make the development of smoking cessation products a priority in accordance with the Family Smoking Prevention and Tobacco Control Act, P.L. 111-31 (Tobacco Control Act); and
• Transfer the evaluation of smoking cessation products from the Division of Anesthetics, Critical Care and Addiction Drug Products to the Office of Hematology and Oncology Products.

We have carefully considered the arguments in each Petition as well as the comments on the Petitions submitted to the docket. For the reasons stated in section II of this response, the Petitioners’ requests are granted in part and denied in part.

I. BACKGROUND

NRT drug products have been marketed in the United States for more than 20 years. The products at issue in these petitions – NRT gum, lozenges, and transdermal patches – were initially approved and marketed as prescription-only treatments to aid smoking cessation. They were switched in the mid-1990s from prescription-only to OTC status.¹²

OTC NRT products are designed to help people stop smoking by supplying a controlled amount of nicotine to ease the withdrawal symptoms associated with a quit attempt. These products were proven to be effective aids to smoking cessation when an individual first stops using cigarettes, and then uses an OTC NRT product for a certain period of time to address the symptoms of withdrawal (up to 12 weeks depending on the product).¹³

Despite the availability of NRT and other smoking cessation drug products, tobacco use continues to be a major public health problem in the United States. Cigarette smoking remains the leading cause of preventable death in the U.S., accounting for approximately 443,000 deaths, or about one of every five deaths, in the U.S. each year.¹⁴ Smoking is a known cause of many adverse health consequences, including cardiovascular disease, lung cancer, and other cancers, and has negative effects on reproduction and early childhood development in children exposed to cigarette smoke.¹⁵ Each year, diseases caused by cigarette smoking cost the health care system $96 billion.¹⁶

On June 22, 2009, the President signed the Tobacco Control Act into law. The Tobacco Control Act provides new authority to FDA to regulate tobacco products, to protect the public health generally, and to reduce tobacco use by minors. While new drug products

¹² In addition, there are two NRT drug products available by prescription only: a nasal spray and an oral inhaler.
¹³ To date, the Agency has not received data supporting the approval of OTC NRT products for any other intended use.
¹⁵ Id.
containing nicotine are reviewed and approved by FDA’s Center for Drug Evaluation and Research (CDER), the Agency has established a new center, the Center for Tobacco Products (CTP), to administer the Tobacco Control Act. We note that our responses to the Petitioners’ requests are not intended to preclude any actions deemed necessary under the Tobacco Control Act.

II. DISCUSSION

A. Requests for Labeling Changes to OTC NRT Drug Products

The following sections discuss three types of labeling changes proposed by the Petitioners. First, we address the argument that certain restrictions currently included in the labeling of OTC NRT products, specifically those related to concomitant use and duration of use, may discourage consumers from using OTC NRT products in an effective manner and should be removed. Second, we address the argument that OTC NRT may be safe and effective for certain additional indications, including indications for long-term use to achieve goals such as maintenance of abstinence; indications for concomitant use; indications for relief of symptoms during periods of temporary abstinence from smoking; and indications involving higher dosage or different rates of delivery. Finally, we address the argument that OTC NRT labeling should be modified to disclose the benefits of NRT use relative to continued cigarette use, and the related argument that NRTs are safe and safer than cigarettes for all smokers, including patients with a history of cardiovascular disease, pregnant women, and adolescents.

1. Request to modify current labeling restrictions on concomitant use and duration of use

Petitioners assert that both consumers and clinicians commonly misunderstand the risks of OTC NRT use, believing that nicotine causes heart disease, cancer, and other diseases, and that as a result NRT is underutilized.\textsuperscript{17} Based on these concerns, Petitioners request a number of modifications to the current labeling of OTC NRT products.

Several of these requests relate to restrictions on the concomitant use of OTC NRT with other NRT products, or with continued tobacco use, including cigarette smoking. Current labeling for OTC NRT products states: “Do not use if you continue to smoke, chew tobacco, use snuff, or use [a different NRT product] or other nicotine containing products.” Current labeling also includes, under “Directions,” the statement: “Stop smoking completely when you begin using [the NRT product].”

Petitioners argue that OTC NRT products can be safely and effectively used to achieve cessation in combination with other NRTs – for example, a user might wear a nicotine-containing patch and chew nicotine-containing gum.\textsuperscript{18} Petitioners also argue that OTC

\textsuperscript{17} UMD Petition at 18-19, 20-21; PHG Petition at 6; NY Petition at 2.
\textsuperscript{18} UMD Petition at 9-10; PHG Petition at 8.
NRT can be safely and effectively used to quit if the user continues to smoke during the initial phase of the quit attempt (so-called “precessation use” of NRT). Based on these arguments, Petitioners request that the current labeling restrictions on concomitant use be removed.

Petitioners also request modifications to current labeling restrictions on duration of use. The labeled dosing period for OTC NRT generally ranges from 8 to 12 weeks, depending on the product. Current labeling includes, under “Directions,” the statement: “Stop using [the NRT product] at the end of [the labeled dosing period]. If you still feel the need to use [the NRT product], talk to your doctor.”

Petitioners argue that OTC NRT can be safely and effectively used beyond the currently labeled treatment period to achieve cessation, and that the product labeling should not restrict users to a specific duration of use.

FDA Response

FDA is unable to make the requested changes to approved drug product labeling through the citizen petition process. Changes to the labeling of OTC NRT products must be supported by submissions from product sponsors to the appropriate New Drug Applications (NDAs). Such submissions must provide sufficient support for the proposed change. Therefore, to the extent Petitioners request that FDA modify certain restrictions in OTC NRT labeling as described above in response to these citizen petitions, this request is denied. The Agency has, however, conducted its own review of the available literature and data on the safety of OTC NRT products and has determined that available evidence supports the modification of certain restrictions in current OTC NRT labeling relating to concomitant use (both with other NRTs and with tobacco) and duration of use. FDA intends to allow the modification of these restrictions based on sponsor submissions as set forth in a Notice of Findings (NOF) to be issued today. The NOF is available at: http://www.archives.gov/federal-register/public-inspection/index.html.

2. Request to create new indications for OTC NRT

In addition to the above requests to modify certain restrictions in current product labeling, Petitioners argue that a variety of new indications should be granted for OTC NRT, as described below.

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19 UMD Petition at 10-11, 12; PHG Petition at 6-7; NY Petition at 3.
20 UMD Petition at 3; PHG Petition at 7, 8; NY Petition at 3-4.
21 UMD Petition at 12-13; PHG Petition at 7.
22 UMD Petition at 3; PHG Petition at 7.
Concomitant use of OTC NRT with other NRT and with tobacco

The UMD petition requests that a new indication be granted for concomitant use with other NRT, asserting that “FDA should expressly state on [NRT] package labeling that combined NRT (patch plus a short-acting form of NRT) has been demonstrated to reduce craving and increase quit rates.” The UMD petition also suggests that a new indication should be granted for concomitant use of OTC NRT with cigarettes, arguing that “incremental reduction in smoking [through pre-cessation use of NRT] is sometimes the first step in successful smoking cessation.”

Long-term use to maintain abstinence

The UMD petition suggests that a separate indication be established for long-term use of NRT to maintain abstinence: “Long-term use of NRT, though contrary to current labeling, is a safe and effective way to sustain smoking cessation.”

Use during periods of temporary abstinence

The NY petition requests that a new indication be granted for use during periods of temporary abstinence unassociated with a quit attempt, asking that FDA “modify the required package labeling and warnings to recognize [that] OTC NRT is appropriate for use in situations of temporary abstinence from cigarettes in order to moderate symptoms of nicotine withdrawal associated with periods of smoking restriction (e.g., in the workplace).”

Increased dosage and rate of delivery of nicotine in OTC NRT therapy

The PHG petition suggests that new indications for NRT might be granted based on increased dosage of nicotine or a different rate of delivery. Specifically, the PHG petition asks that FDA “be willing to review data on whether tobacco cessation products that deliver higher doses or are calibrated to deliver doses at a different rate will improve the efficacy of these products without imposing an undue safety risk.”

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23 UMD Petition at 10; see also PHG Petition at 8 (“FDA should consider data regarding whether some combinations of smoking cessation products...would increase the number of people who successfully quit using tobacco products”).
24 UMD Petition at 10; see also PHG Petition at 7 (“Studies show that incremental reduction in smoking may be beneficial and that pre-cessation NRT further increases quitting success”), NY Petition at 3.
25 UMD Petition at 12; see also NY Petition at 3 (“long-term use of NRT can be appropriate for highly dependent smokers in order to maintain abstinence from smoking”).
26 NY Petition at 2; see also UMD Petition at 12 (“use of NRT for temporary abstinence may...mak[e] a quit attempt with NRT more likely”).
27 PHG Petition at 7.
FDA Response

FDA is unable to make Petitioners’ requested changes to OTC NRT labeling through the citizen petition process. Such changes must be supported by an application from a sponsor providing sufficient evidence for the new indications. To the extent that a sponsor might seek to rely on the literature cited in the citizen petitions, that literature does not appear to be sufficient to support the requested new indications at this time. Furthermore, while the literature cited in the NOF supports the labeling changes described in the NOF, that literature is not sufficient to support Petitioners’ requested new indications at this time.

Sponsors seeking new indications for OTC NRT products should submit supplements to their NDAs providing the appropriate support for their products’ safety and effectiveness for the proposed indications. To the extent Petitioners request that FDA be open to reviewing data submitted by sponsors in support of new indications, and that FDA work with sponsors to develop those indications, those requests are granted. The Agency has been and remains open to reviewing data relating to the new indications described above (and any others), and will work with sponsors based on their submissions to develop new indications for OTC NRT.

Petitioners cite no studies supporting new indications for use of OTC NRT during periods of temporary abstinence, or for use at increased doses or rate of delivery of nicotine. Petitioners cite a number of studies, however, in support of their requests for new indications related to concomitant use and use beyond the labeled period of up to 12 weeks. With respect to these studies, the Agency provides the following comments for informational purposes only.

Indication for concomitant use with other NRT

As noted above, the UMD Petition requests that a new indication for concomitant use with other NRT be added to the labeling of OTC NRT products. Petitioners first assert that “recalcitrant and heavy smokers in particular benefit from using a combination of NRT products in a manner inconsistent with the mandatory product labeling.” The Petition cites four sources for this statement: the Department of Health and Human Services, Public Health Service report *Treating Tobacco Use and Dependence: Clinical Practice Guideline* (Updated 2008) (CPG), and reviews by Sweeney, Fagerstrom and Stead, none of which is a report of a randomized clinical trial.

The page number noted in the UMD Petition directs the reader to a point in the CPG that does not pertain to the statement made in the petition. Elsewhere, the CPG does recommend combination treatments at the discretion of the physician; however, the recommendation is based on a meta-analysis the methods for which are not elucidated.

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28 FDA’s response is limited to an assessment of these indications as additional indications for already-approved OTC NRT drug products.
29 UMD Petition at 9.
The CPG report is a practice guideline. There is no indication from the CPG that data exist to support the statement that combination therapy is particularly helpful for heavy or recalcitrant smokers.

The Sweeney paper is a review of five published studies. The paper does not give any information about whether the subjects in the studies reviewed were heavy or recalcitrant smokers. Furthermore, some of the studies reviewed are less than convincing due to the lack of a factorial design. Although this review could be viewed as generally supportive of the idea of concomitant use, it does not provide convincing scientific evidence that combined use of OTC NRT is effective, especially for heavy or recalcitrant smokers.

Fagerstrom reviews four studies on the effect of combined therapy (nicotine gum and patch) on withdrawal symptoms. The studies reviewed did include smokers of at least 10 cigarettes per day; however, Fagerstrom did not perform a comparison between the results for heavier and lighter smokers, such as might have supported the contention in the UMD Petition that combination therapy is particularly effective for heavy or recalcitrant smokers.

The Stead paper is also a review article. It gives overviews of a number of different studies regarding OTC NRT, some of which pertain to concomitant use; however, it provides no specific information, data, or evidence about differential effectiveness for heavy or recalcitrant smokers.

The UMD Petition also cites the CPG in support of its claim that “combination use of NRT increases abstinence rates,” and that “NRT combinations are especially helpful for highly dependent smokers or those with a history of severe withdrawal.” The PHG Petition cites the CPG on the same point, noting that the CPG “discuss[es] a number of studies that show that some patients benefit from the combined use of smoking cessation products, including different NRT products.” The UMD Petition cites Table 3.3 of the CPG to support these points. This table does not contain any information that would support combination use of OTC NRT. However, Table 3.2 describes a meta-analysis of multiple studies, some of which pertain to combination use of OTC NRT (the PHG Petition refers to the same meta-analysis). The specific details about the studies encompassed by the meta-analysis are not provided, so it cannot be determined whether these studies demonstrated improved long-term abstinence rates with combination therapy as compared to standard treatment, or showed improvements across different subpopulations. In addition, the study by Piper et al., which is also cited by the UMD Petition, notes that “[m]eta-analyses that attempt to account for interstudy differences may yield conclusions that conflict markedly with large-scale head-to-head trials.”

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30 The recommendations contained in the CPG relate to the practice of medicine, which FDA does not regulate. The recommendations contained in a practice guideline would not be viewed by FDA as evidence of the safety or effectiveness of a drug product.
31 UMD Petition at 9 (quoting CPG).
32 PHG Petition at 8.
these reasons, the meta-analysis described in the CPG is not sufficient evidence to support the conclusion that combination use of OTC NRT promotes long-term abstinence or is especially helpful for specific subpopulations of smokers.

Regarding the claim that “NRT combinations are especially helpful for highly dependent smokers or those with a history of severe withdrawal,” the UMD Petition refers to studies by Piper, Kozlowski, Sweeney and Fagerstrom.\textsuperscript{34} Sweeney and Fagerstrom are both cited in Table 3.2 of the CPG as well.

The paper by Piper is a report of a randomized, double-blind, placebo-controlled clinical trial to assess the relative efficacies of five smoking cessation therapies, some of which are combinations, using head-to-head comparisons. The results of this study provide some support for the contention that the nicotine patch combined with the nicotine lozenge is superior to either product alone; however, only a small subset of patients in the study received patch plus lozenge therapy and the endpoint studied (odds ratio) is difficult to interpret. Therefore, the study does not provide sufficient evidence to support an independent assessment of patch plus lozenge combination therapy. We also note that the differential effectiveness of the therapies in the study was not determined for highly dependent smokers or those with a history of severe withdrawal. Thus, the study does not provide evidence that combined use of OTC NRT is particularly helpful for a specific subpopulation of smokers, as the UMD Petition claims.

The paper by Kozlowski is a consensus statement that contains no supporting data. The section of the paper to which the UMD Petition cites is a sample statement to consumers. This paper provides no evidence that that combined use of OTC NRT is particularly helpful for a specific subpopulation of smokers.

The review by Sweeney and that by Fagerstrom are discussed above. As previously noted, these studies do not provide convincing scientific evidence that combined use of OTC NRT is effective, especially for highly dependent smokers or those with a history of severe withdrawal.

\textit{Indication for concomitant use of OTC NRT with tobacco to support a “reduce to quit” approach}

As noted above, the UMD Petition requests a new indication for concomitant use of OTC NRT with tobacco, asserting that “[r]esearch shows that the use of NRT during incremental reduction in smoking is related to increased likelihood of long-term abstinence.”\textsuperscript{35} In support of this assertion, the UMD Petition states that “a meta-analysis of four studies” concluded that precession patch treatment produced an increase in quit rates.\textsuperscript{36} Although these four studies are cited, the meta-analysis to which the petition refers is not. The PHG Petition also states that “[s]udies show that incremental reduction

\textsuperscript{34} UMD Petition at 9.
\textsuperscript{35} UMD Petition at 10.
\textsuperscript{36} Id.
in smoking may be beneficial and that pre-cessation NRT further increases quitting success.”37 The UMD and PHG Petitions both cite studies by Schuurmans, Rose, Bullen, and Wang in support of their arguments on concomitant use of NRT with tobacco.

The Schuurmans paper describes a randomized, controlled trial of healthy smokers that measured whether 2-week pre-treatment with the nicotine patch influences withdrawal symptoms or success rate of subsequent smoking cessation using nicotine patches. This study was well-designed and demonstrated that patients who received pre-treatment with the nicotine patch were more likely to achieve sustained abstinence than patients who did not. However, information on incremental reduction, or “reduce to quit” practices, was not presented, because patients were instructed not to change their smoking behavior during pre-treatment. Therefore, this study does not support the points made in the UMD and PHG Petitions regarding use of OTC NRT for “reduce to quit” attempts.

The Rose paper describes a double-blind factorial trial exploring the effect of the use of the nicotine patch for two weeks prior to a target quit date. The results of the study did show that “precession nicotine patch treatment was associated with a significantly higher rate of continuous smoking abstinence at 4 weeks, regardless of cigarette condition.”38 However, these results are difficult to extrapolate to a real-world scenario because the patients in the trial were given an experimental treatment (mecamylamine) after quit day. Also, the results do not provide data or information on incremental reduction, because subjects were encouraged to continue to smoke cigarettes, which were provided as a part of the study, at their normal rates until quit day. The study does provide some evidence that pre-cession treatment could promote cessation, but it does not support the concept of “reduce to quit.”

The Bullen paper describes an uncontrolled, clinic-based pilot study of fourteen patients. Its principal aim was to test the tolerability of using OTC NRT while smoking, not the effectiveness of such treatment for smoking cessation. In FDA’s view it does not provide any valid evidence of the effectiveness of pre-cession treatment for smoking cessation or incremental reduction. Therefore, this study does not support the arguments made in the UMD and PHG Petitions regarding incremental reduction.

The Wang paper is a report of a meta-analysis of systematic reviews, randomized, controlled trials, and available economic analyses of “cut down to quit” methods. It does describe precession use of OTC NRT in patients who were not yet ready to quit, but it does not provide information about the efficacy of precession treatment in smokers who were motivated and ready to quit. It also does not address the question of whether incremental reduction leads to successful quit attempts. The data presented regarding the benefits of reduction showed “small increments of improvement” in “some domains.”39

37 PHG Petition at 7.
In FDA’s view, this level of evidence is not sufficient to support the claims in the UMD and PHG Petitions regarding incremental reduction.

The NY Petition also makes claims regarding concomitant use of OTC NRT with tobacco as part of a “reduce to quit” regimen. Specifically, the NY Petition cites the Wennike study, stating Wennike found that subjects using OTC NRT “decreased the number of cigarettes smoked daily and achieved a higher smoking cessation rate” than those who did not use NRT. The NY Petition also cites the Batra study, stating Batra found that subjects using NRT “sustained greater reductions in consumption and point prevalence abstinence from smoking” than those who did not use NRT.

The Wennike paper describes a randomized, controlled trial evaluating the effect of nicotine gum versus placebo with regard to smoking reduction and smoking cessation in smokers not motivated or not able to quit. The study did demonstrate a higher rate of sustained reduction and a higher rate of quitting for nicotine gum-treated subjects compared to placebo-treated subjects, but the rates for both of these outcomes were quite low. Also, the authors “observed a tendency towards a decrease in motivation to reduce or quit in failures during the study period... In contrast, motivation to maintain reduction or stay quit increased among successful reducers and abstainers.” Because the great majority of study subjects were unsuccessful at reducing or quitting, the overall effect of the treatment could be viewed as de-motivating most of the subjects. Thus, although this study does support the statement in the NY Petition, FDA would not view the data presented as sufficient evidence to support a claim of reduction to quit.

The Batra paper describes a randomized, double-blind, placebo-controlled trial of smokers who were not ready to quit, but who wanted to reduce their smoking intensity. The study evaluated the effectiveness of nicotine gum for incremental reduction. The data support the contention that nicotine gum treatment, with instructions to cut down smoking as much as possible, was more effective than placebo in promoting quitting. This study was also part of the meta-analysis presented in the Wang paper cited by the UMD and PHG Petitions. The analysis presented in the Wang paper showed that 9% of the nicotine-treated group in the Batra study achieved 6 months of abstinence, compared to 1% of the placebo-treated group. Thus, this study does provide some support for the statement in the NY Petition, although the results are not overwhelmingly positive.

**Indication for long-term use to maintain abstinence**

As noted above, the UMD Petition argues that long-term use of OTC NRT is a safe and effective way to sustain abstinence. The UMD Petition states that “[s]tudies show that

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40 NY Petition at 3.
41 Id.
43 UMD Petition at 12.
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. In support of this statement, the UMD Petition cites studies by Nides, Murray, Hughes, and Henningfield; this section of the UMD Petition also cites the CPG, which relies on the same four studies.

Nides et al. report the results of a randomized trial of participants enrolled in the Lung Health Study’s (LHS) 12-week, cognitive-behavioral, group smoking cessation program. The results do not confirm the statement in the UMD Petition that long-term use of OTC NRT supports continued abstinence. Some of the long-term abstinent former smokers in the study continued to use nicotine gum for a prolonged period, but there was no control group in the study that did not have access to nicotine gum. Thus, it is unclear whether long-term use alone is what led to sustained abstinence. The data presented actually suggest that study participants who used nicotine gum during the study were more likely to relapse than those who did not. In addition, patients who received cognitive-behavioral therapy were able to discontinue nicotine gum use without relapse. Finally, the claims in the UMD Petition regarding safety of long-term use of OTC NRT are not supported by the trial report, because the authors do not comment on safety.

Murray et al. reported the results of a randomized, controlled trial of participants in the LHS, including safety information on the long-term use of nicotine gum, but their study does not confirm the statement made in the UMD Petition that “nearly one-third of Lung Health Study participants who remained cigarette-free after 2 months continued to use nicotine gum safely.” The trial did provide data on the safety of nicotine gum use for as long as five years and indicated that use of nicotine gum for such an extended period of time is safe, but it did not present any data regarding the effectiveness of long-term use of OTC NRT to support continued abstinence.

The Hughes study examined the effect of cost on long-term use of nicotine gum, but did not present any data or information about the safety or effectiveness of long-term use of OTC NRT. Additionally, the authors refer to the results of another study, which found that “among smokers who quit with free nicotine gum, 35-50% become behaviorally dependent on the gum, i.e., use the gum beyond the recommended 3-4 months . . . [and] cessation of gum use after the 3- to 4-month period was not associated with an increased rate of relapse to smoking; thus, procedures to eliminate use of the gum beyond the recommended period would appear to be indicated.” These results contradict the assertion in the UMD Petition that long-term use “supports continued abstinence.” This study cannot be construed to support the claims made in the UMD Petition regarding the safety and effectiveness of long-term use of OTC NRT to support continued abstinence.

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44 UMD Petition at 13.
45 Id. and n.41.
The article by Henningfield is a review that summarizes the scientific rationale for nicotine medications. The paper briefly touches on long-term use of nicotine medications, but does not contain any data that support the claims made in the UMD Petition regarding the safety and effectiveness of long-term use of OTC NRT to support continued abstinence.

The NY Petition also claims that “long-term use of NRT can be appropriate for highly dependent smokers in order to maintain abstinence from smoking.” In support of this statement, the NY Petition cites a paper by Hajek that presents the results of an analysis of the extent of long-term use of different NRT in smokers already engaged in routine smoking cessation treatment, and the effect of cost on their utilization of NRT. This study confirms that some smokers use NRT for an extended period of time (more than 1 year after their quit date), but does not present any data to show that long-term use of OTC NRT is particularly helpful for highly dependent smokers.

3. Request to modify labeling to state the risks and benefits of OTC NRT use relative to continued cigarette use, and that OTC NRT use is safe and safer than cigarettes

Petitioners request a number of labeling changes that involve comparisons between the use of OTC NRT and cigarette smoking. For example, the NY Petition asks that FDA “modify labeling requirements in order to fully disclose to smokers the benefits of OTC NRT use relative to continued cigarette use, with risks [of OTC NRT] compared to risks associated with continued cigarette use.” Similarly, the UMD Petition states that “product labeling should reflect the potential health risks associated with use of NRT as compared to the significant negative health risks caused by smoking.” Finally, the PHG Petition asks that FDA “re-evaluate currently approved product labels” to provide potential users of OTC NRT with information on “the relative risks of these products and continued tobacco use.”

In a related argument, the NY Petition asks that FDA “modify the required package labeling” to state that “OTC NRT is safe for use by smokers and safer for use than continued cigarette use.” The UMD Petition states that “NRT is safe in the overwhelming majority of the population,” and that “[i]n virtually all conditions, use of NRT is vastly safer than smoking.”

Further, the NY Petition argues that the use of OTC NRT is safer than cigarette use for smokers with cardiovascular disease (CVD), for pregnant smokers, and for adolescent

47 NY Petition at 3.
48 NY Petition at 1.
49 UMD Petition at 3; see also id. at 18-21 (arguing that these labeling changes will improve understanding of NRTs among both consumers and clinicians).
50 PHG Petition at 6.
51 NY Petition at 2, 3.
52 UMD Petition at 8.
smokers ages 12 and older. The petition implies that changes should be made to current labeling provisions directed at these populations, stating that smokers in these groups “would benefit from more accurate comparisons regarding the relative safety of OTC NRT and cigarettes.” The UMD petition also argues that smokers with CVD should be encouraged to use OTC NRT to quit “because there is no increased risk of heart disease or acute cardiovascular outcomes associated with use of NRT,” adding that “the label requirement indicating that those with heart disease should seek medical advice prior to using NRT should be eliminated.”

With regard to label comparisons between OTC NRT and smoking, therefore, Petitioners make three requests. Two are explicit requests for modifications to OTC NRT labeling: one to compare the risks and/or benefits of NRT to the effects of smoking, and one to state that NRT use is safe and safer than cigarettes. In addition, Petitioners suggest that labeling provisions related to the use of OTC NRT by smokers with CVD, pregnant smokers, and adolescent smokers be modified.

FDA Response

As noted above in section II.A.2., FDA is unable to make the requested changes to approved drug product labeling through the citizen petition process. FDA is open to reviewing any data sponsors would like to submit in support of the above or related labeling changes for OTC NRT products.

Modification of labeling to compare OTC NRT and smoking

For informational purposes, the Agency provides the following comments on Petitioners’ requests that OTC NRT labeling be modified to include comparisons between the use of OTC NRT and cigarette smoking.

With regard to the request for a label statement comparing the risks and/or benefits of NRT use to the effects of cigarette smoking: As an initial consideration, we note that the concept of “cigarette smoking” or “continued cigarette use” could encompass a variety of different scenarios, from a few cigarettes smoked per week to a pack a day. In light of this, it might be difficult to design a study that would support addition of the requested statement to the product label. To the Agency’s knowledge, the individual risk-benefit ratio of OTC NRT products relative to continued smoking has not been elucidated.

With regard to the request that the labeling of OTC NRT products be modified to state that these products are safe and safer than cigarettes for all smokers: This too is a very broad statement and one that may be difficult to support. The variation among

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53 NY Petition at 3.
54 NY Petition at 3.
55 UMD Petition at 14-15. This petition seeks no “specific changes to FDA policy” relating to the use of OTC NRT in pregnant women or adolescents. Id. at 17-18.
consumers and among populations of consumers who use OTC NRT products may make it difficult to support a broad statement that these products are safe for all smokers and, in all cases, safer than cigarettes.

With regard to the studies cited by Petitioners in support of the above requests, the Agency provides the following comments for informational purposes only.

In support of the argument that OTC NRT is “vastly” safer than smoking in “virtually all conditions,” the UMD Petition cites a report by the Royal College of Physicians (RCP). The report has limitations that are similar to those of the CPG: Although it makes recommendations to physicians as to how they should treat patients who are unable to quit smoking, and contains broad policy recommendations regarding the regulation of nicotine-containing products, it does not present any data or evidence to support the statement in the UMD Petition. And despite the fact that it contains a few general statements that echo the claim in the petition that OTC NRT is safer than smoking, this report mostly focuses on the dangers of smoking and tobacco use rather than the safety of OTC NRT.

The NY Petition also argues that OTC NRT is safer than smoking, citing the book Nicotine Safety and Toxicity, edited by Benowitz, to support a statement that “[t]he risks associated with nicotine delivered without the smoke toxins are lower by several orders of magnitude.” The NY Petition also cites a study by McNeill to support a statement that “the benefits and risks of OTC NRT use should be weighed against the benefits and risks of continued use of cigarettes.”

Nicotine Safety and Toxicity presents the findings of a number of published studies related to the safety and toxicity of nicotine. These publications cover various topics related to the effects of nicotine, including its relationship to cancer, cardiovascular disease, and reproductive issues. The book presents data specific to these conditions, many of which are exacerbated by smoking. The conclusion of Nicotine Safety and Toxicity, written by Dr. Benowitz, supports the statement in the NY Petition; however, there are no data in the book that quantify the risks associated with nicotine alone as compared to nicotine delivered via cigarette smoke.

The review by McNeill et al. discusses the public health system in the United Kingdom. McNeill makes many similar arguments in her paper as are made in the NY Petition; however, none of these arguments are supported by data or scientific evidence. In FDA’s view, the McNeill paper does not present adequate evidence that the benefits and risks of OTC NRT should be weighed against the benefits and risks of continued smoking.

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57 UMD Petition at 8.
58 Rennard, SI, Daughton, D, and J Windley, Toxicity of Nicotine Replacement in Patients with Coronary Artery Disease, in Nicotine Safety and Toxicity, ed. N Benowitz, 52 (Oxford University Press, 1998).
59 Id.
Modification of labeling provisions related to specific populations

With regard to the specific populations referenced in connection with Petitioners’ arguments comparing OTC NRT use to smoking, FDA responds as follows.

Patients with a History of CVD

OTC NRT drug products have pharmacologic effects on the cardiovascular system, including increases in heart rate and cardiac contractility, the constriction of coronary arteries, and transient increase in blood pressure. Although it is possible that OTC NRT is safer than cigarettes for patients with CVD, it must be noted that OTC NRT is far from universally effective in helping smokers quit; therefore, the risk of adding OTC NRT to ongoing smoking must also be considered.

In high-risk patients with CVD, non-pharmacologic smoking cessation is optimal, but for those who cannot accomplish this, OTC NRT may be a valid option. The current “Warnings” section of the labeling for OTC NRT products includes the following statement directed at those consumers who have CVD: “Ask a doctor before use if you have . . . heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.”

To ensure safe use by consumers with CVD, warnings directing these consumers to consult their health care providers before beginning OTC NRT therapy are necessary to protect their health and safety. Note that the warning does not preclude the use of OTC NRT in this population; rather, it encourages consumers with CVD to consult their health care providers before using OTC NRT. A health care practitioner can recommend use of OTC NRT products to any patient for whom the benefit of OTC NRT therapy appears to outweigh the risk.

For informational purposes, the Agency provides the following comments on studies cited by Petitioners.

The NY Petition asserts that use of OTC NRT is safer than cigarette use for smokers with CVD, and cites papers by Hillis, Marsh, McRobbie, Murray, Joseph (two studies) and Nicotine Safety and Toxicity to support this claim. The Hillis paper cited in the text of the NY Petition was not included in the bibliography, and we were unable to review it.

The Marsh paper describes a randomized, open-label trial intended to compare the safety profile of nicotine gum versus nicotine lozenges in smokers with CVD. This study did not compare use of OTC NRT with continued smoking, as more than 90% of the

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61 NY Petition at 3.
62 The NY Petition provided only the author’s name and year of publication, and did not identify a specific publication.
participants continued to smoke during the study. The lack of a non-smoking arm makes a comparison between the use of OTC NRT and smoking for patients with CVD impossible.

The McRobbie article is an advice column for health care professionals discussing use of NRT in patients with CVD. Although the authors of this article advocate for the use of OTC NRT for patients with CVD, they assume that it will be used on a short-term basis and that patients will not continue to smoke. Given the lack of data or scientific evidence presented, in FDA’s view this article does not support the assertion in the NY Petition that OTC NRT is safer than smoking for patients with CVD.

As noted above in section II.A.2, the study conducted by Murray et al. was of patients enrolled in the LHS. The LHS did not specifically enroll smokers with CVD. In fact, patients were excluded if they had a heart attack or stroke in the previous two years, angina, or heart failure. Therefore, the Murray study cannot support any statement about the benefits of OTC NRT for patients with CVD.

The 2003 article by Joseph et al. in the American Journal of Cardiovascular Drugs presents a summary of quitting strategies for smokers with CVD. The article summarizes much of the literature regarding use of OTC NRT for patients with CVD and notes that smoking-induced changes in cardiac risk factors are reduced with cessation, even if NRT is used. However, given the lack of data or scientific evidence, in FDA’s view this article does not support the contention in the NY Petition that OTC NRT is safer than smoking for patients with CVD.

Another 2003 review by Joseph, in Progress in Cardiovascular Diseases, reviews the literature on use of the nicotine patch in patients with CVD and concludes that use of the nicotine patch does not increase risks of serious adverse events compared with placebo in patients with CVD. This review provides support for the statement in the NY Petition for certain types of NRT, but cannot be construed to support a broad statement about the safety of all types of NRT for smokers with CVD.

The chapter in Nicotine Safety and Toxicity devoted to the toxicity of nicotine in patients with CVD draws the conclusion that “transdermal nicotine in . . . patients [with CVD] would currently be regarded as an appropriate therapeutic option.”63 For this chapter, the authors reviewed many of the same studies cited by Joseph, and their review suffers from similar limitations. The chapter provides support for the statement in the NY Petition for certain types of OTC NRT, but cannot be construed to support a broad statement about the safety of all types of OTC NRT for smokers with CVD.

The UMD Petition asserts that the CPG “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." The UMD Petition notes that the CPG cites seven studies in support of these statements. The seven sources cited include *Nicotine Safety and Toxicity* and McRobbie, discussed above. As discussed in section II.A.2 above, the CPG is a clinical guideline. The CPG does not present data in support of Petitioners' statements; rather, it cites papers that have similar limitations to those cited by the NY Petition (e.g., review articles, lack of data, poor design, no direct examination of the association between OTC NRT and CVD, small study size). For these reasons, the CPG would not be considered by FDA to provide sufficient evidence to support a broad statement about the safety of all types of NRT for smokers with CVD.

The UMD Petition also cites a report by the Royal College of Physicians (RCP), quoting the report as stating that "the 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." In support of this statement the RCP cites many of the same studies as the other references discussed in this response (including Marsh, Batra, and Joseph). The RCP also notes that clinical trials in healthy people lack the power to detect an adverse effect of OTC NRT in patients with cardiovascular disease. Much of the evidence cited by the RCP pertains to smokers without CVD or is confounded by the positive effects of smoking cessation. For these reasons, the statement from the RCP cited in the NY Petition does not support the conclusion that OTC NRT is safe for all patients with CVD.

*Pregnant Women*

Data are limited on the use of OTC NRT drug products by pregnant women, the outcome of this use on their infants, and the childhood development patterns of their children. Although some of the pharmacologic effects of OTC NRT drug products on the mother and developing fetus are known, the full range of consequences or risks to the developing fetus are not fully understood. The Agency has reviewed reproductive toxicology studies of *in utero* nicotine exposure in multiple animal species during the period of major organogenesis. Extrapolating from the animal data on nicotine exposure and considering the smoking data in humans, the Agency believes that chronic nicotine exposure may represent some risk in humans for embryo-fetal lethality, but likely presents little risk for teratogenic or adverse developmental effects.

While smoking has clearly been associated with fetal harm, the contribution of nicotine has not been clearly delineated. There are numerous other constituents of cigarette smoke that may be major contributing factors to the harm caused by smoking. There have been no long-term studies on the behavioral or neurodevelopmental effects of

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64 UMD Petition at 14.
65 Id.
67 Id.
nicotine exposure during pregnancy comparing NRT to smoking or to quitting without pharmacologic treatment.

In 2001 FDA revised the pregnancy warning on the labeling for OTC NRT drug products to state, in the WARNINGS section of the drug facts labeling:

If you are pregnant or breast-feeding only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Pregnancy presents a unique set of circumstances: a finite period of time during which both the pregnant woman and the developing fetus may be exposed to any substances consumed, and the risks and benefits may be different for each. Although the available data are insufficient to clearly establish the relative risks of OTC NRT versus continued smoking in the developing fetus, smoking is clearly associated with fetal harm. The 2001 labeling statement was developed based on the Agency’s belief that total abstinence from smoking and nicotine is the safest alternative for a pregnant woman and for the developing fetus. The Agency sought to convey, however, that while the risks of OTC NRT are unknown, use of OTC NRT may be safer than smoking during the finite period of pregnancy.

Given the lack of data on the safety and efficacy of OTC NRT for pregnant women and the developing fetus, FDA believes the existing pregnancy labeling is appropriate.

For informational purposes, the Agency provides the following comments on studies cited by Petitioners.

The NY Petition asserts that use of OTC NRT is safer than cigarette use for smokers who are pregnant, and cites data from Oncken (2 studies) and Nicotine Safety and Toxicity to support this statement.\(^{68}\)

Oncken’s 1996 publication reported the results of a randomized study of 29 pregnant women who either smoked or stopped smoking and chewed nicotine gum. The study concluded that “short-term use of nicotine gum delivers less nicotine than usual cigarette smoking in pregnant women” (emphasis added).\(^{69}\) This study provides some support for the statement in the NY Petition, but only with regard to nicotine gum. Furthermore, the study was very small and the subjects used NRT for a very short duration (5 days) and at sub-therapeutic levels (6 pieces of gum per day). It is difficult to extrapolate support for the overall safety of OTC NRT in pregnant women from the results of this study.

\(^{68}\) NY Petition at 3.
Oncken’s 1997 paper describes a randomized, single-dose trial of the nicotine patch in pregnant women. The investigators found similar nicotine exposure for pregnant women who smoked and those who used the nicotine patch, and greater loss of fetal heart rate reactivity in women using the nicotine patch. Also, the women in the study only wore the nicotine patch for 8 hours on one day. It is difficult to draw any conclusions about the overall safety of OTC NRT in pregnant women based on the results of this study.

In *Nicotine Safety and Toxicity*, Oncken et al. suggest that NRT is probably less harmful than smoking, but also state that “there is no known safe dose of nicotine that can be administered during pregnancy.” If OTC NRT is necessary during pregnancy, the authors state it “should be considered if the likelihood of smoking cessation appears low without such measures...[and] if it is necessary to begin nicotine replacement therapy, the sooner used and discontinued, the better.” These statements only refer to use of nicotine gum. Oncken et al. also conclude that the safety of a transdermal patch during pregnancy “has not been established.” Thus, the findings reviewed in *Nicotine Safety and Toxicity* do not conclusively support the statement in the NY Petition.

### Adolescents

Published studies on adolescents have not demonstrated the efficacy of any OTC NRT as an aid to smoking cessation in adolescents. It is known that adolescents can become addicted to nicotine and that they will have withdrawal symptoms that make quitting difficult. It is also known that once a youth begins smoking, he or she is more likely than an adult to become addicted, and that most adult smokers began smoking before age 18. In children under age 18, use of currently available OTC NRT does not appear to be associated with severe adverse events, but the available studies involve a limited number of subjects.

The current labeling for OTC NRT products reflects the lack of data on safety and efficacy for adolescents under age 18. The DIRECTIONS section of the labeling for nicotine gum and patch products states, “if you are under 18 years of age, ask a doctor before use.” The Agency believes this language is appropriate given the limited data

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71 Id.
72 Id.
75 The DIRECTIONS section of the labeling for nicotine lozenges has the following additional statement regarding adolescents: “No studies have been done to show if this product will work for you.” This statement was added to the label after the sponsor completed postmarketing pediatric studies required under
available. We note that current labeling does not preclude the use of OTC NRT drug products in adolescents. A physician can recommend use of these products to any patient for whom the benefit appears to outweigh the risk.

For informational purposes, the Agency provides the following comments on studies cited by Petitioners.

The NY Petition asserts that use of OTC NRT is safer than cigarette use for smokers who are adolescents (age 12 years and older), and cites studies by Smith, McNeill and Moolchan to support this claim. The Smith study cited in the text of the NY Petition was not included in the bibliography, and we were unable to review it.

As noted above, the article by McNeill is a review. None of the arguments in the paper are supported by data or scientific evidence. Thus, the McNeill paper does not support the statement in the NY Petition regarding the safety of OTC NRT relative to smoking for adolescents. Similarly, the paper by Moolchan et al., although a report of a randomized, controlled trial, does not present any data regarding the safety of OTC NRT relative to continued smoking. Neither article, therefore, supports the statement in the NY Petition regarding the safety of OTC NRT relative to cigarette smoking for adolescent smokers.

In summary, although evidence suggests that the use of currently available OTC NRT products may be safer than the use of cigarettes for many smokers, the Agency believes that given the lack of data on use of these products by pregnant women and adolescents, the existing labeling statements referring these consumers to their health care providers for advice are appropriate. In addition, the possible pharmacological effects of OTC NRT on consumers with CVD lead us to conclude that the specific warnings directed to this population are appropriate. The labeling for OTC NRT products also contains specific warnings for consumers who have stomach ulcers or diabetes, or are taking prescription medications for depression or asthma. The Agency believes these warnings are necessary to protect the health and safety of these patients.

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the Pediatric Research Equity Act (PREA). Because the lozenge was submitted for approval later than the other forms of OTC NRT, it is the only OTC NRT product subject to PREA.

76 NY Petition at 3.

77 The NY Petition provided only the author’s name and year of publication, and did not identify a specific publication.
B. Requests for FDA Policy Changes in the Review and Approval of OTC NRT Drug Products

Petitioners make several requests related to the way in which OTC NRT products are reviewed and approved for marketing. First, all three petitions request that FDA evaluate the risks of OTC NRT and other smoking cessation products against the risks of continued smoking.\(^78\)

In addition, the PHG Petition requests that FDA make the following policy changes:

- Initiate a program whereby the Agency will collaborate with manufacturers of smoking cessation products to identify appropriate trial design;\(^79\)
- Promote and encourage the development of innovative smoking cessation products in accordance with Section 918 of the FD&C Act, as amended by the Tobacco Control Act;\(^80\) and
- Transfer the evaluation of NRT from the Division of Anesthesics, Critical Care and Addiction Drug Products to the Office of Hematology and Oncology Products.\(^81\)

Petitioners argue that these changes are necessary to “ensure that [FDA’s] requirements and activities create appropriate incentives to develop and make available the most effective smoking cessation products and that effective products are approved so that the maximum number of lives can be saved.”\(^82\)

1. Evaluating the risks of OTC NRT use as compared to continued smoking rather than placebo

Petitioners argue that the risks associated with use of OTC NRT should be evaluated by comparison to the risks associated with continued tobacco use, rather than by comparison to a placebo.\(^83\) Petitioners first claim that FDA “has not given adequate consideration to the risks of continued tobacco use when it evaluated, approved and established the conditions for sale and use of currently marketed products,” including OTC NRT products.\(^84\) In addition, Petitioners appear to argue that using continued smoking as the comparator for the risks of OTC NRT will result in changes to product labeling that will increase the use of NRT products and decrease tobacco-related harms: “If patients are being warned only of the risks of the smoking cessation product, they are not getting an accurate picture. Patients and their doctors may be choosing not to use smoking

\(^78\) PHG Petition at 1, 5-6; UMD Petition at 3, 5, 21; NY Petition at 2.
\(^79\) PHG Petition at 2, 8-9.
\(^80\) PHG Petition at 2, 9.
\(^81\) PHG Petition at 2, 9.
\(^82\) PHG Petition at 1; see also UMD Petition at 21, NY Petition at 2.
\(^83\) PHG Petition at 1, 5-6; UMD Petition at 3, 5, 21; NY Petition at 2.
\(^84\) PHG Petition at 6; see also UMD Petition at 21.
cessation products because of the risks listed in the labeling without regard to the risk of continued tobacco use. 85

FDA Response

As noted above, Petitioners' first argument relates to FDA's process for the review and approval of new drug products. The assertion is that FDA failed to adequately consider the risks of continued tobacco use when it evaluated and approved OTC NRT products for marketing. This is not the case.

In evaluating new drug products, FDA uses studies in which the drug is compared to placebo to determine which of the adverse events experienced by study participants are related to the study drug. In evaluating a study in which a drug is compared to placebo, the Agency is not comparing the risks of the drug to the risks of placebo. Instead, we compare the adverse events reported by the patients treated with the drug to the adverse events reported by the patients treated with placebo so that we can understand which adverse events are likely to be drug-related. This allows us to elucidate the safety profile of the drug. For example, specific drug-related adverse events associated with the use of OTC NRT products include the hiccoughs reported by patients using transmucosal nicotine products and the unusual, intense dreams reported by patients using transdermal nicotine products (which deliver nicotine around the clock, including while the patient is sleeping). Patients and providers need to be aware of the potential side effects of specific products to make an informed choice between various treatment options, and to the extent reactions occur, to be able to understand that those reactions might be linked to the patient's medication.

In addition, FDA's evaluation of new drug products is based on the intended use proposed by the sponsor. 86 OTC NRT products were originally submitted for approval as aids to smoking cessation. Therefore, FDA evaluated the safety and effectiveness of these products in achieving smoking cessation. To do this, FDA had to use data from randomized, controlled clinical trials showing that OTC NRT is more effective at helping patients quit smoking than either a placebo or another product. To prove that OTC NRT products are safe and effective for this proposed intended use, they cannot be compared to continued smoking.

The risks of continued smoking are, however, considered by FDA as part of the benefit-risk profile of the drug. 87 In other words, the fact that a product reduces the likelihood that patients will continue to smoke is taken into account in evaluating all safety and effectiveness data associated with the product. In effect, the risk of continued smoking is already taken into account in the way NRT products are evaluated. This will continue to be the case in future evaluations of NRT product candidates and indications.

85 PHG Petition at 6; see also UMD Petition at 21, NY Petition at 2.
86 See 21 CFR 314.50(c)(2).
87 See 21 CFR 312.84.
As further noted above, Petitioners also appear to argue for the use of continued smoking as a comparator as a means of changing the description of risks in product labeling – specifically, of characterizing the risks of OTC NRT products as lower than those associated with smoking.\textsuperscript{88} As noted above in our responses to the requests described in Section II.A.3, the Agency is unable to make such changes to approved drug product labeling through the citizen petition process. Changes to the labeling of OTC NRT products must be supported by submissions from product sponsors. We also note that the concerns outlined in Section II.A.3 regarding the difficulty of supporting labeling changes comparing the risks and/or benefits of NRT to the effects of smoking, or stating that NRT use is safe and safer than cigarettes, apply here as well.

For these reasons, Petitioners’ request that FDA evaluate the risks of OTC NRT products against the risks of continued smoking is denied, to the extent that request would interfere with FDA’s evaluation of drug product candidates by comparison to placebo (or another drug product with the same indication) as described above. To the extent Petitioners request that FDA take the risks of continued smoking into account in the analysis of risks and benefits associated with the evaluation of a particular product candidate for a particular indication, Petitioners’ request is granted.

2. \textit{Initiation of a program whereby the Agency will collaborate with manufacturers of smoking cessation products to identify appropriate trial design}

The PHG Petitioners argue that current “limitations on smoking cessation products and how they are used” may have created a disincentive for manufacturers to develop new treatments for smoking cessation.\textsuperscript{89} The PHG Petitioners request that FDA, “offer to meet with manufacturers early in the development phase to help them develop the appropriate clinical trials with appropriate clinical endpoints.”\textsuperscript{90} Specifically, petitioners encourage FDA to consider accepting “alternate clinical endpoints,” such as an endpoint involving reduced consumption of cigarettes, and surrogate endpoints such as those used in fast track and accelerated approval processes.\textsuperscript{91}

\textbf{FDA Response}

FDA regularly meets with sponsors of all types of drug products to offer advice on clinical trial protocols and design at all phases of the drug development process.\textsuperscript{92} Sponsors may request a formal meeting, and FDA often informally interacts with sponsors on questions related to investigational products. FDA is open to meeting with manufacturers of OTC NRT products to help develop appropriate trial designs for innovative products and help select appropriate endpoints to support proposed

\textsuperscript{88} PHG Petition at 6.
\textsuperscript{89} PHG Petition at 8.
\textsuperscript{90} PHG Petition at 8.
\textsuperscript{91} PHG Petition at 8-9.
\textsuperscript{92} See 21 CFR 312.82.
indications. Petitioners’ request that FDA be willing to meet with manufacturers to help them develop their clinical trials is granted.

With regard to “alternate clinical endpoints”: FDA has been and remains open to considering endpoints other than smoking cessation in studies of OTC NRT products, and recommends that sponsors discuss those endpoints with the appropriate review division early in the drug development process. With regard to fast track and accelerated approval processes and the acceptance of surrogate endpoints as part of those processes: to qualify for fast track status, a drug must be intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs.\textsuperscript{93} FDA does consider tobacco dependence to be a serious or life-threatening condition. Whether a product addresses an unmet medical need, and thereby qualifies for accelerated approval processes including reliance on surrogate endpoints, must be resolved by FDA on a case-by-case basis. FDA has been and remains open to discussing fast track and accelerated approval processes with the sponsors of OTC NRT products. Therefore, Petitioners’ request that FDA consider “alternate clinical endpoints” and surrogate endpoints in the approval of new products and indications is granted.

We note that when the NDAs for OTC NRT products were originally submitted, the endpoint typically used in the trials that supported approval was a one-month quit – that is, a one-month cessation of smoking. This endpoint was accepted in place of the ultimate clinical goal of OTC NRT therapy under the approved intended use, namely, permanent cessation of smoking. Any new smoking cessation product submitted under an NDA would be able to use the trial designs allowed for previous products, including the endpoint of a one-month quit.

3. \textit{Prioritizing the development of smoking cessation products in accordance with the Family Smoking Prevention and Tobacco Control Act.}

The PHG Petition requests that FDA “make the development of smoking cessation products a priority.”\textsuperscript{94} Petitioners cite section 918 of the FD&C Act (21 U.S.C. 387r) as amended by the Tobacco Control Act, stating that section 918 “directed FDA to promote and encourage the development of innovative smoking cessation products and treatments.”\textsuperscript{95} As part of their argument that FDA prioritize the development of smoking cessation products, Petitioners suggest that FDA should “send a signal to industry that it will help them ensure that currently marketed products are used effectively by smokers.”\textsuperscript{96}

\textsuperscript{94} PHG Petition at 2.
\textsuperscript{95} PHG Petition at 9.
\textsuperscript{96} PHG Petition at 9.
FDA Response

The Agency has prioritized the development of smoking cessation products in accordance with section 918 of the FD&C Act.

Section 918 instructs the Secretary of the Department of Health and Human Services (the Secretary) to consider taking certain actions with regard to smoking cessation products, including designating these products as fast track products eligible for accelerated approval; approving the extended use of NRTs for the treatment of tobacco dependence; and approving new indications for NRTs, “such as for craving relief or relapse prevention.” Section 918 also requires the Secretary to submit a report to Congress, after consultation with recognized scientific, medical, and public health experts, that “examines how best to regulate, promote, and encourage the development of innovative products and treatments (including nicotine-based and non-nicotine based products and treatments) to better achieve, in a manner that best protects and promotes the public health – (A) total abstinence from tobacco use; (B) reductions in consumption of tobacco; and (C) reductions in the harm associated with continued tobacco use.”

The section 918 report to Congress will be submitted in the near future. This report will discuss FDA’s actions and current policies relating to fast track processes and new indications for NRT products, in addition to the regulation of “innovative products and treatments” for achieving abstinence, reductions in consumption, and reductions in harm. On December 17, 2012, FDA held a public hearing under 21 CFR Part 15 to gather input from all interested stakeholders on the full range of issues raised by section 918, and the input received at that hearing (including comments submitted to the associated docket) has been taken into account in the development of the report to Congress. Finally, this response to three citizen petitions related to OTC NRT, along with the accompanying NOF, effectively lifts several restrictions in the labeling of those products related to concomitant use and duration of use. It is hoped that this action will signal not only to industry but to all interested stakeholders that the Agency is committed to the effective use of OTC NRT products.

Thus, by means of the upcoming publication of the section 918 report to Congress; the Part 15 hearing on section 918; this response to three citizen petitions related to OTC NRT products, and the accompanying NOF; and many related internal actions within the Agency, Petitioners’ request that FDA prioritize the development of smoking cessation products is granted.

4. **Transfer of the evaluation of smoking cessation products from the Division of Anesthesia, Analgesics and Addiction Products (DAAAP) to the Office of Hematology and Oncology Products (OHOP)**

The PHG Petition asserts that smoking cessation products should be evaluated not by the Division of Anesthesia, Analgesics and Addiction Products (DAAAP), but by the Office
of Hematology and Oncology Products (OHOP). Petitioners argue that OHOP is better positioned to review smoking cessation products because OHOP “has the most expertise regarding the dangers of continued tobacco use,” “has experience with efforts to encourage the development of new drugs,” and “has substantial experience reviewing drugs when the risks of the drug must be weighed against the risk of a deadly disease.”

FDA Response

Smoking cessation products are intended for use as aids to quitting smoking, not for the treatment of cancer. OHOP is staffed by oncologists who are experts at evaluating cancer treatments or treatments that prevent cancer. They are not experts in addiction or the treatment of addiction, which is the type of expertise required to evaluate NRT and other smoking cessation products. Although smoking is linked to cancer, smoking cessation treatments are very different from cancer prevention treatments. NRT products, for example, treat the consequences of nicotine addiction and withdrawal. The reviewers in DAAAP are experts in the treatment of addiction and are best equipped to review the safety and effectiveness of such products. The reviewers in the Division of Nonprescription Clinical Evaluation (DNCE) have expertise in evaluating the safety of products for use by consumers in a nonprescription environment. Prescription-only smoking cessation treatments are properly located in DAAAP, and nonprescription treatments such as OTC NRT are properly located in DNCE with collaborative input from DAAAP. Petitioners’ request is denied.

C. Access to OTC NRT Drug Products

The NY Petition requests that we withdraw the following conditions stated in the approval letter for the OTC marketing of Nicorette (nicotine polacrilex gum) 2 milligrams (mgs) and 4 mgs: (1) Restriction of distribution of the products to drugstores, mass merchandisers, and supermarkets where OTC drugs are sold (while prohibiting distribution in other channels, including convenience stores and vending machines); and (2) Prohibition on marketing of “trial size” or “sample” packs (e.g., packs small enough to be priced competitively with cigarettes). Similarly, as general requests applicable to all OTC NRT, both the NY Petition and the UMD Petition request that we allow OTC NRT products to be sold in any retail outlet where cigarettes are sold, and to be packaged in a “sample size,” e.g., a size that can be competitively priced with cigarettes and/or that contains an amount of OTC NRT product that would typically be consumed in a 24-hour period. The NY Petition also requests that we allow OTC NRT products to

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97 PHG Petition at 2, 9. The PHG Petition refers to the Office of Oncology Products, which was formerly the name of OHOP, and the Division of Anesthesics, Critical Care and Addiction Drug Products, which was formerly the name of DAAAP.
98 PHG Petition at 9.
99 NY Petition at 1.
100 NY Petition at 1-2; UMD Petition at 4.
101 NY Petition at 1-2; UMD Petition at 15 - 17. Although the PHG Petition does not explicitly address these issues, a footnote on Page 7 of the PHG Petition states that “it may also be appropriate for FDA to examine other factors, such as pricing and availability issues and their impact on usage.”
be advantageously positioned relative to cigarettes and tobacco products to promote the sale of the NRT products.\textsuperscript{102}

Petitioners argue that restrictions on the types of retail outlets that may sell OTC NRT constrain the utilization of these products,\textsuperscript{103} and that these limitations on retail outlets and on package size contribute to “less effective use of NRT.”\textsuperscript{104}

FDA Response

1. **Retail Outlets Selling OTC NRT Products**

Petitioners’ request that we allow the sale of Nicorette and other OTC NRT drug products in all retail locations where cigarettes are sold has effectively been granted. Hoechst Marion Roussel, Inc. (HMR), the original sponsor of the NDAs for OTC Nicorette gum (2 mgs and 4 mgs), voluntarily committed to restrict distribution to drugstores, mass merchandisers, and supermarkets where other OTC drugs are sold, and not to sell OTC Nicorette in convenience stores and vending machines. This restriction was included by HMR in the marketing plan for Nicorette when the product was switched from prescription to OTC status in February 1996.\textsuperscript{105} In August 1996, SmithKline Beecham Consumer Healthcare (SBCH) (now a part of GlaxoSmithKline Consumer Healthcare), which had acquired the OTC Nicorette NDAs, notified the Agency that the company was removing the distribution restriction for convenience stores from the marketing plan and intended to begin selling Nicorette in convenience stores immediately.\textsuperscript{106} SBCH felt that this change would benefit the public health by providing greater access to OTC NRT therapy for populations who might not have easy access to drugstores, mass merchandisers, or supermarkets. SBCH also noted that convenience store owners had committed to verifying the age of purchasers, and the company was confident that compliance with age restrictions on the sale of Nicorette would be maintained. Finally, SBCH pointed out that other forms of OTC NRT did not have the same retail restrictions. Because the retail restrictions in Nicorette’s marketing plan were not one of the requirements for approval, but were a voluntary commitment made by SBCH with which the Agency had concurred, the change was accepted by the Agency without objection.

Therefore, because the retail restrictions for Nicorette were a voluntary commitment on the part of the sponsor, FDA did not “limit the availability of NRT to certain establishments”\textsuperscript{107} or place “restrictions on the types of outlets that can offer OTC NRT.”\textsuperscript{108} Rather, Nicorette’s sponsor voluntarily committed to these restrictions and was able to easily remove them without Agency objection. Sponsors of other forms of OTC

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\textsuperscript{102} NY Petition at 2.

\textsuperscript{103} NY Petition at 2.

\textsuperscript{104} UMD Petition at 15.

\textsuperscript{105} See February 9, 1996, letter from FDA to HMR approving Nicorette gum available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/96/018612s022_Nicorette_approv.PDF.

\textsuperscript{106} See August 12, 1996, letter from SBCH to FDA (on file with FDA).

\textsuperscript{107} UMD Petition at 15.

\textsuperscript{108} NY Petition at 2.
NRT did not commit to the same retail restrictions, so their distribution has not been limited. For the reasons set forth above, Petitioners’ request is effectively granted.

2. Package Size of OTC NRT Products

Petitioners also request that OTC NRT drug products be permitted to be sold in “sample” or “daily” units (containing an amount of NRT that would typically be consumed in a 24-hour period). The NY Petition argues that large package size contributes to the low utilization of OTC NRT.\(^{109}\) The UMD Petition suggests that smaller pack sizes would enable smokers to “experiment” with different forms of NRT, and choose the method they prefer.\(^{110}\) Petitioners also argue that smaller pack sizes would remove a financial barrier to the purchase of OTC NRT for low-income smokers.\(^{111}\)

The UMD Petition goes on to argue that a small package size would also allow smokers to abstain for limited periods of time where smoking is forbidden or otherwise problematic (the UMD Petition gives the example of a grandmother visiting her grandchildren; another example would be a smoker who needs to get through a plane ride without smoking). While these periods of temporary abstinence from smoking would be unrelated to a quit attempt, Petitioners assert that they “may lead to a desire or interest in cessation if the NRT shows promise.”\(^{112}\)

FDA has evaluated package sizes for OTC NRT products in light of the approved intended use for these products, which is as aids to smoking cessation. When reviewing proposed smaller package sizes of OTC NRT, FDA has taken into consideration the fact that consumers will vary in the amount of product they use over the course of a quit attempt. In addition, FDA is aware that individual consumers may taper their doses at different rates and having access to packages of varying sizes provides more flexibility, especially near the end of a treatment course. There are also advantages to having a smaller package size for consumers who may be traveling or who have forgotten their supply of OTC NRT. A smaller package size would allow these consumers to continue treatment without bearing a significant cost.

For these reasons, FDA has approved OTC NRT products in package sizes that would allow consumers to purchase a part of the treatment regimen, rather than requiring them to buy the full course of treatment at once. For example, FDA has approved a 20-unit package of nicotine gum\(^{113}\), a 28-unit package of nicotine lozenges\(^{114}\), and a 7-unit package of the nicotine patch.\(^{115}\) In addition, FDA has approved a 10-unit package of

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\(^{109}\) NY Petition at 2.
\(^{110}\) UMD Petition at 15.
\(^{111}\) UMD Petition at 15, 16-17.
\(^{112}\) UMD Petition at 16.
\(^{113}\) See, e.g., http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/018612s043,020066s024LTR.pdf.
\(^{114}\) See, e.g., http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021330s005ltr.pdf.
\(^{115}\) See, e.g., http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/020165Orig1s028ltr.pdf.
nicotine gum. All of these package sizes are consistent with the products’ approved use as aids to smoking cessation. These smaller package sizes are intended to enable consumers to purchase enough of the drug product to sustain or complete a quit attempt, and the labeling reflects this indication.

Therefore, to the extent Petitioners request that FDA approve smaller package sizes for OTC NRT to provide consumers with greater convenience and flexibility in carrying out a quit attempt, that request is granted.

To the extent the UMD Petition requests approval of a smaller package size for an existing OTC NRT product that would be intended for use during periods of temporary abstinence unrelated to a quit attempt, that request is denied. As discussed above in section II.A.2, FDA is unable to approve new indications for approved drug products through the citizen petition process. Sponsors seeking new indications for OTC NRT products should submit supplements to their NDAs providing appropriate support for those new indications.

3. Positioning of OTC NRT Products in Retail Outlets

With respect to the NY Petition’s request that we issue a policy stating that OTC NRT products may be advantageously positioned in stores relative to cigarettes and other tobacco products, we note that the location of OTC NRT drug products on store shelves is not a condition for FDA approval of these products, nor is it within FDA’s current authority. The sale and distribution of cigarettes is regulated by the individual states and the placement of products is often determined by individual stores. Consequently, we are unable to grant Petitioners’ request that we issue a policy stating that OTC NRT products may be advantageously positioned in stores relative to cigarettes and other tobacco products. The request is, therefore, denied.

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116 The minimum daily dose of nicotine gum is 9 pieces. Depending on the number of cigarettes smoked before quitting and the stage of the quitting process, 10 pieces of gum may be sufficient for a full day’s treatment. However, some consumers will chew more than 10 pieces of gum in one day. For these reasons, FDA required a disclaimer on the front of the 10-piece package noting that “this package may not be a full day’s supply.”

117 See, e.g., http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/018612s061_020066s042lbl.pdf; http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021330s005lbl.pdf; and http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020165s024lbl.pdf. In addition, the packaging for the 10-pack of nicotine gum notes that the package “is intended to start or continue a quit attempt.”
III. CONCLUSION

For the reasons stated in section II of this response, the Petitioners’ requests are granted in part and denied in part. The following paragraphs summarize our responses.

Labeling Changes

Request to modify certain labeling restrictions on concomitant use and duration of use for OTC NRT: 118

 Denied to the extent these labeling changes are requested as a response to these citizen petitions. However, FDA intends to allow modification of these restrictions based on sponsor submissions as set forth in a Notice of Findings to be issued today. The NOF is available at http://www.archives.gov/federal-register/public-inspection/index.html.

Request to allow new indications for OTC NRT: 119

 Denied to the extent these labeling changes are requested as a response to these citizen petitions. Granted to the extent Petitioners request that FDA remain open to reviewing data from sponsors in support of these indications, and working with sponsors to develop them.

Request to modify labeling to state the risks and benefits of OTC NRT use relative to continued cigarette use, and that OTC NRT use is safe and safer than cigarettes, including in certain specified populations (individuals with CVD, pregnant women, and adolescents): 120

 Denied. FDA remains open to reviewing data from sponsors in support of these labeling changes.

Policy Changes

Request to evaluate the risks of OTC NRT and other smoking cessation products as compared to continued smoking rather than placebo: 121

 Denied, to the extent Petitioners’ request would interfere with FDA’s evaluation of drug product candidates by comparison to placebo (or another drug product with the same indication). Granted, to the extent Petitioners request that FDA take the risks of continued smoking into account in the analysis of risks and benefits associated with the evaluation of a particular product candidate for a particular indication.

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118 UMD Petition at 3, 9-11, 12-13; PHG Petition at 6-7, 8; NY Petition at 3-4.
119 UMD Petition at 10, 12; PHG Petition at 7, 8; NY Petition at 2, 3.
120 UMD Petition at 3, 8, 14-15, 17-18, 18-21; PHG Petition at 6; NY Petition at 2, 3.
121 PHG Petition at 1, 5-6; UMD Petition at 3, 5, 21; NY Petition at 2.
Request to collaborate with sponsors of smoking cessation products to identify trial designs.\textsuperscript{122}

Granted.

Request to consider “alternate clinical endpoints” and surrogate endpoints in the approval of new smoking cessation products and indications.\textsuperscript{123}

Granted.

Request to prioritize the development of smoking cessation products in accordance with section 918 of the FD&C Act.\textsuperscript{124}

Granted.

Request to transfer evaluation of smoking cessation products from the Division of Anesthesia, Analgesics and Addiction Products (DAAAP) to the Office of Hematology and Oncology Products (OHOP).\textsuperscript{125}

Denied.

\textbf{Access to OTC NRT Products}

Request to allow the sale of OTC NRT in all retail outlets where cigarettes are sold.\textsuperscript{126}

Granted.

Request to allow smaller package sizes of OTC NRT.\textsuperscript{127}

Granted to the extent Petitioners’ request is to approve smaller package sizes to provide consumers with greater convenience and flexibility in carrying out their quit attempt. Denied to the extent Petitioners’ request is to approve a smaller package size that would be intended for use during periods of temporary abstinence unrelated to a quit attempt.

Request to allow OTC NRT products to be advantageously positioned in stores relative to cigarettes and other tobacco products.\textsuperscript{128}

Denied.

\textsuperscript{122} PHG Petition at 8.
\textsuperscript{123} PHG Petition at 8-9.
\textsuperscript{124} PHG Petition at 2, 9.
\textsuperscript{125} PHG Petition at 2, 9.
\textsuperscript{126} NY Petition at 1-2; UMD Petition at 4.
\textsuperscript{127} NY Petition at 1-2; UMD Petition at 15-17.
\textsuperscript{128} NY Petition at 2.
We remain committed to meeting with NDA holders interested in developing new indications for currently approved OTC NRT products corresponding to your requests, and/or reviewing data submitted by NDA holders to support any of your proposed labeling changes. We remain committed to providing safe and effective therapies for individuals who are trying to quit smoking.

Sincerely,

Janet Woodcock
Director
Center for Drug Evaluation and Research