urine to determine compliance of isoniazid (INH) medication. FDA is seeking panel input on the safety and effectiveness of isoniazid test strips.

FDA intends to make background material available to the public no later than 2 business days before the meeting. If FDA is unable to post the background material on its Web site prior to the meeting, the background material will be made publicly available at the location of the advisory committee meeting, and the background material will be posted on FDA's Web site after the meeting. Background material is available at *http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm*. Scroll down to the appropriate advisory committee meeting link.

3. On page 13347, in the third column, the section entitled ''Procedure'' is corrected to read as follows:

Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person on or before April 16, 2013. On April 25, 2013, oral presentations from the public regarding Methotrexate Test Systems will be scheduled between approximately 9:15 a.m. and 9:45 a.m.; regarding phencyclidine (PCP) Test Systems between approximately 1:55 p.m. and 2:25 p.m.; and regarding Isoniazid Test Systems between approximately 4:15 p.m. and 4:45 p.m. Those individuals interested in making formal oral presentations should notify the contact person and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation on or before April 8, 2013. Time allotted for each presentation may be limited. If the number of registrants requesting to speak is greater than can be reasonably accommodated during the scheduled open public hearing session, FDA may conduct a lottery to determine the speakers for the scheduled open public hearing session. The contact person will notify interested persons regarding their request to speak by April 9, 2013.

Dated: March 27, 2013.

Jill Hartzler Warner,

Acting Associate Commissioner for Special Medical Programs.

[FR Doc. 2013–07568 Filed 4–1–13; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2013–N–0341]

Modifications To Labeling of Nicotine Replacement Therapy Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that we have concluded that certain statements set forth in the FDA-approved labels of over-the-counter nicotine replacement therapy products, related to concomitant use with other nicotine-containing products and duration of use, can be modified. In light of currently available evidence, these statements are no longer believed to be necessary in their current form to ensure the safe and effective use of over-the-counter nicotine replacement therapy products for their approved intended use as aids to smoking cessation. We encourage the submission of supplemental new drug applications (labeling supplements) to modify these statements as described in this notice.

ADDRESSES: Submit labeling supplements to the Center for Drug Evaluation and Research, Food and Drug Administration, Central Document Room (CDR), 5901–B Ammendale Rd., Beltsville, MD 20705–1266. Copies of the recommended revisions to product labeling may be requested from the Center for Drug Evaluation and Research's Division of Nonprescription Clinical Evaluation, 10903 New Hampshire Ave., Bldg. 22, Stop 5411, Silver Spring, MD 20993, 301–796–2080. Copies of published studies that can be used to support labeling supplements will be on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and can be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Doris J. Bates, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 4417, Silver Spring, MD 20993, 301–796–1040, FAX: 301–796–9721, email: *doris.bates@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Background

A. Smoking and Tobacco Dependence

Tobacco use is the leading preventable cause of death and disease in the United States. According to an estimate by the Centers for Disease Control and Prevention, cigarette smoking causes 443,000 deaths each year in the United States, including nearly 50,000 deaths per year from involuntary exposure to tobacco smoke (Ref. 1). Smoking is known to cause multiple cancers, heart disease, stroke, complications of pregnancy, chronic obstructive pulmonary disease, and many other diseases that, on average, shorten smokers' lifespans by 14 years (Ref. 2).

Surveys show that approximately 70 percent of current smokers want to stop smoking, and nearly half of all smokers make a quit attempt each year (Ref. 3). Unfortunately, dependence on nicotine—the primary addictive substance in tobacco—is a chronic disease that often requires repeated intervention and multiple quit attempts to overcome. As a result, only a small percentage of smokers successfully quit each year (Ref. 3).

B. Over-the-Counter Nicotine Replacement Therapies

Nicotine replacement therapy (NRT) products are designed to help people stop smoking by supplying controlled amounts of nicotine to ease the withdrawal symptoms associated with a quit attempt. NRT products do not contain all of the carcinogens and other harmful constituents that are found in cigarette smoke. There are currently three types of NRT products approved by FDA for over-the-counter (OTC) use as smoking cessation aids: Nicotine gum, transdermal nicotine patch, and nicotine lozenge products.[1] The nicotine gum and patch products were originally approved through the new drug application (NDA) process between 1984 and 1992. Both the gum and the patch were initially available by prescription only; these products were switched from prescription to OTC status between 1996 and 2002. The nicotine lozenge and mini-lozenge were approved directly for OTC use in 2002 and 2009, respectively.

Currently, the FDA-approved labeling for OTC NRT products instructs consumers that they should stop smoking when they begin using the product and that they should not use

[1] A nicotine spray and a nicotine inhaler have also been approved as smoking cessation aids. However, these NRT products are available by prescription only and are therefore outside the scope of this notice.

the product in combination with cigarettes or other nicotine-containing products (including other NRT products). The labeling also recommends a specific duration of use of up to 12 weeks, depending on the product, and instructs consumers to stop using the NRT product at the end of that period. Consumers are advised to consult a doctor if they feel they need to continue using the NRT product for longer than the recommended course of treatment.

In recent years, a number of stakeholders in the public health and health care provider communities have suggested that these labeling statements act as barriers to the effective use of OTC NRT products for smoking cessation. These stakeholders have argued that the statement advising against concomitant use of the NRT products with cigarettes may cause some smokers to abandon quit attempts if they experience a lapse (e.g., if they have a cigarette while using an NRT product). Stakeholders have also argued that use of more than one NRT product (e.g., patch plus gum) is more effective for some smokers than use of a single NRT product in achieving cessation, and that current labeling discourages such use. With regard to duration of use, stakeholders have argued that the use of OTC NRT products beyond the labeled treatment period may increase the chances of quitting for certain smokers.[2] These stakeholders have asserted that there are no safety concerns associated with concomitant use of OTC NRT products with other nicotine-containing products, or with the use of OTC NRT products for longer than the labeled duration of use.

Over the nearly 30 years since NRT products were first approved, evidence has accumulated to suggest that the current labeling provisions on concomitant use and duration of use may no longer be necessary to ensure the safe use of OTC NRT products for smoking cessation. Based on this evidence, FDA has concluded that the current labeling statements for OTC NRT products concerning concomitant use and duration of use can be modified as described in this document. We invite the products' sponsors to submit supplemental NDAs (labeling supplements) to modify these statements in the labeling of their drug products. To facilitate the process, the Agency has identified revisions to the labeling of OTC NRT products that can be included in these labeling supplements. Those revisions are set forth in section II.

II. Proposed Revisions to the Labeling of OTC NRT Products

A. Concomitant Use of OTC NRT Products With Cigarettes or Other Nicotine-Containing Products, Including Other NRT

The ''Drug Facts'' section of the label for OTC NRT products currently contains two statements relating to the use of these products with other nicotine-containing products. The first statement is found under the ''Do not use'' subheading of the ''Warnings'' section. It instructs consumers not to use the OTC NRT product if they ''continue to smoke, chew tobacco, use snuff, or use [a different NRT product] or other nicotine containing products.'' This statement was included in the labeling because at the time during which these products were switched to OTC use, there was little reliable data on the safety of the higher levels of nicotine that would result from using NRT products in combination with other nicotine-containing products. The second statement appears under the ''Directions'' section, and tells consumers to ''stop smoking completely when you begin using the [NRT product].'' This statement was included in the label because in the clinical trials that were conducted for the original NRT product approvals, individuals who stopped smoking completely when they began using NRT were more likely to quit.

Since we first approved NRT products for OTC use, a number of studies have been conducted that provide information on the safety of using NRT products in combination with other nicotine-containing products. Many of these studies focused on the effects of using NRT products while smoking. For example, there have been studies on the use of NRT products by smokers who were not immediately interested in quitting (see Hatsukami et al., 2007), on the use of NRT products as an aid to smoking reduction (see Wennike et al., 2003; Batra et al., 2005), and on the use of NRT products before initiating a quit attempt (Lindson and Aveyard, 2011). In addition, several studies have been conducted on the use of higher-than-standard-dose NRT products (Tønnesen et al., 1999) and on the concomitant use of more than one type of NRT product (see Bohadana et al., 2000; Piper et al., 2009).

Upon reviewing the published reports of these and other studies, we have determined that the concomitant use of OTC NRT products with cigarettes or with other nicotine-containing products does not raise significant safety concerns. The published literature contains few reports of adverse events arising from the use of NRT products while smoking or using another NRT product. The Agency also notes that few adverse events have been reported in studies of concomitant use conducted under the investigational new drug (IND) process, which involves mandatory reporting of adverse events.

Accordingly, we are announcing that the statements in the current labeling of OTC NRT products relating to concomitant use of those products with other nicotine-containing products can be modified. The following specific changes to the current approved ''Drug Facts'' labeling are recommended:

- *Warnings.* The ''Do not use'' subheading and the statement underneath it instructing consumers not to use the NRT product if they ''continue to smoke, chew tobacco, use snuff, or use [a different NRT product] or other nicotine containing products'' should be deleted.
- *Directions.* The third bullet should be revised from ''stop smoking completely when you begin using the [NRT product]'' to ''begin using the [NRT product] on your quit day.''

B. Duration of Use of OTC NRT Products

Currently, the labeling of OTC NRT products recommends a specific duration of use of up to 12 weeks, depending on the product. For example, the ''Drug Facts'' section of the label for nicotine gum and lozenge products recommends that those products be used for 12 weeks; the label for certain nicotine patch products recommends a duration of use of 8 weeks, others 10 weeks. These labeled durations of use reflect the treatment periods that were studied in the clinical trials that supported the switch of these products to OTC status. Because NRT products treat the acute withdrawal symptoms associated with a quit attempt, and those symptoms typically diminish over time, most of the clinical trials conducted to support approval were short—generally between 6 and 12 weeks in length.

In addition to recommending a specific duration of use, current OTC NRT product labels direct consumers to stop using the product at the end of the recommended treatment period and to talk to a doctor if they feel they need to use the product longer. This statement was included in the labeling because at the time of the first prescription-to-OTC switch, there was insufficient data to

[2] In this notice, the Agency takes no position on the effectiveness of NRT products when used concomitantly with other nicotine-containing products, or when used for longer than the labeled duration of use.

address the Agency's concern that consumers could potentially become dependent on NRT products.

In the years since NRT products became available for OTC use, a number of studies have examined the use of NRT products over periods longer than 12 weeks. We have reviewed the published literature on this longer-term use of NRT products and have not identified any safety risks associated with such use. A well-known and highly regarded study on the effects of long-term use of NRT products is the Lung Health Study, in which almost 6,000 smokers were given access to free nicotine gum for up to 5 years (see Murray et al., 1996). In this study, over 1,000 subjects were still using the gum after 1 year. The adverse effects of long-term nicotine gum use reported by these subjects were described as minor and transient, and there was no correlation between long-term gum use and cardiovascular events. A followup study found that long-term ad lib use of nicotine gum neither increased nor decreased the Lung Health Study subjects' likelihood of developing cancer (see Murray et al., 2009). Other informative studies on the effects of long-term use of NRT products include a 52-week study of NRT product use in which nearly half of the subjects used two or more OTC NRT products in combination (see Joseph et al., 2011), and a trial involving the use of nicotine patches for 6 to 12 months by nonsmokers with mild cognitive impairment (see Newhouse et al., 2012). Both of these studies had high rates of completion and reported few adverse events from long-term use of NRT products.

We also note that although any nicotine-containing product has the potential to be addicting, based on the available evidence, currently marketed OTC NRT products do not appear to have significant potential for abuse or dependence. A 2010 review of historical reports made to the Agency's Adverse Event Reporting System and to the Substance Abuse and Mental Health Services Administration's Drug Abuse Warning Network between 1984 and 2009 suggested that NRT products have a low potential for abuse. Several published studies have also found that the abuse liability and dependence potential of NRT products is low, especially compared to cigarettes (see West et al., 2000; Houtsmuller et al., 2002).

Accordingly, we are announcing that the statement in the labeling of OTC NRT products directing consumers to stop using the NRT product at the end of the recommended treatment period can be modified. The following specific change to the current approved ''Drug Facts'' labeling is recommended:

- *Directions.* The last bullet should be revised from ''it is important to complete treatment. Stop using the [NRT product] at the end of [x] weeks. If you still feel the need to use [the NRT product], talk to your doctor'' to ''it is important to complete treatment. If you feel you need to use [the NRT product] for a longer period to keep from smoking, talk to your health care provider.''

C. Summary of Proposed Labeling Revisions

In light of currently available evidence on the concomitant use of OTC NRT products with cigarettes or other nicotine-containing products, and on the use of OTC NRT products beyond the labeled period of treatment, the following changes to the ''Drug Facts'' labeling of OTC NRT products are recommended:

Current drug facts labeling	Proposed drug facts labeling
Warnings	
Do not use: • if you continue to smoke, chew tobacco, use snuff, or use [a different NRT product] or other nicotine containing products.	None. The ''Do not use'' statement would be deleted.
Directions	
• stop smoking completely when you begin using the [NRT product] .... • it is important to complete treatment. Stop using the [NRT product] at the end of [x] weeks. If you still feel the need to use [the NRT product], talk to your doctor.	• begin using the [NRT product] on your quit day. • it is important to complete treatment. If you feel you need to use [the NRT product] for a longer period to keep from smoking, talk to your health care provider.

We have determined that these labeling revisions may be addressed through a changes being effected (CBE) supplement under 21 CFR 314.70(c)(6).

We are also recommending conforming changes to other FDA-approved labeling for OTC NRT products, such as product user guides and leaflets. Copies of the recommended changes to these other labeling items may be obtained from the Center for Drug Evaluation and Research's Division of Nonprescription Clinical Evaluation (see **ADDRESSES**).

III. Conclusions

We have determined that the current OTC NRT products can be used safely and effectively for their approved intended use as aids to smoking cessation with the labeling modifications identified in section II. We encourage the submission of labeling supplements for these drug products. These supplements should modify the labeling statements concerning concomitant use and duration of use as described in section II. The requirement for data to support these labeling changes may be met by citing the published literature we relied on in preparing this notice. A list of the published literature and reprints of the reports will be available for public inspection in the Division of Dockets Management (see **ADDRESSES**). It is unnecessary to submit copies and reprints of the reports from the listed published literature. We invite applicants to submit any other pertinent studies and literature of which they are aware.

IV. Published Literature Supporting Proposed Labeling Revisions

The published literature we have relied on in making the determinations contained in this notice is listed in this section of the document. Copies of the published literature will be on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at *http://www.regulations.gov*.

1. Batra, A., et al., ''Smoking Reduction Treatment With 4-Mg Nicotine Gum: A Double-Blind, Randomized, Placebo-Controlled Study,'' *Clinical*

Pharmacology and Therapeutics, 78(6):689–96, 2005.
2. Benowitz, N.L., et al., ''Suppression of Nicotine Intake During Ad Libitum Cigarette Smoking by High-Dose Transdermal Nicotine,'' *Journal of Pharmacology and Experimental Therapeutics,* 287(3):958–62, 1998.
3. Blondal, T., et al., ''Nicotine Nasal Spray With Nicotine Patch for Smoking Cessation: Randomised Trial With Six Year Follow Up,'' *BMJ,* 318(7179):285–8, 1999.
4. Bohadana, A., et al., ''Nicotine Inhaler and Nicotine Patch as a Combination Therapy for Smoking Cessation,'' *Archives of Internal Medicine,* 160(20):3128–34, 2000.
5. Bolliger, C.T., et al, ''Smoking Reduction With Oral Nicotine Inhalers: Double Blind, Randomised Clinical Trial of Efficacy And Safety,'' *BMJ,* 321(7257):329–33, 2000.
6. Bullen, C., et al., ''Precessation Nicotine Replacement Therapy: Pragmatic Randomized Trial,'' *Addiction,* 105(8):1474–83, 2010.
7. Dale, L.C., et al., ''High-Dose Nicotine Patch Therapy. Percentage of Replacement and Smoking Cessation,'' *JAMA,* 274(17):1353–58, 1995.
8. Etter, J.F., et al., ''Nicotine Replacement to Reduce Cigarette Consumption in Smokers Who Are Unwilling to Quit: A Randomized Trial,'' *Journal of Clinical Psychopharmacology,* 22(5):487–95, 2002.
9. Etter, J.F., et al., ''Postintervention Effect of Nicotine Replacement Therapy on Smoking Reduction in Smokers Who Are Unwilling to Quit: A Randomized Trial,'' *Journal of Clinical Psychopharmacology,* 24(2):174–79, 2004.
10. Etter, J.F., et al., ''Nicotine Gum Treatment Before Smoking Cessation—A Randomized Trial,'' *Archives of Internal Medicine,* 169(11):1028–34, 2009.
11. Hajek, P., et al., ''Dependence Potential of Nicotine Replacement Treatments: Effects of Product Type, Patient Characteristics, and Cost to User,'' *Preventive Medicine,* 44(3):230–34, 2007.
12. Hall, S.M., et al., ''Extended Treatment of Older Cigarette Smokers,'' *Addiction,* 104(6):1043–52, 2009.
13. Hatsukami, D., et al., ''Effects of High Dose Transdermal Nicotine Replacement in Cigarette Smokers,'' *Pharmacology, Biochemistry, and Behavior,* 86(1):132–39, 2007.
14. Horst, W.D., et al., ''Extended Use of Nicotine Replacement Therapy to Maintain Smoking Cessation in Persons With Schizophrenia,'' *Neuropsychiatric Disease and Treatment,* 1(4):349–55, 2005.
15. Houtsmuller, E.J., et al., ''Flavor Improvement Does Not Increase Abuse Liability of Nicotine Chewing Gum,'' *Pharmacology, Biochemistry, and Behavior,* 72(3):559–68, 2002.
16. Hughes, J.R., et al., ''A Randomized, Controlled Trial of NRT-Aided Gradual Vs. Abrupt Cessation in Smokers Actively Trying to Quit,'' *Drug and Alcohol Dependence,* 111(1–2):105–13, 2010.
17. Joseph, A.M., et al., ''Chronic Disease Management for Tobacco Dependence,'' *Archives of Internal Medicine,* 171(21):1894–1900, 2011.
18. Lerman, C., et al., ''Genetic Variation in Nicotine Metabolism Predicts the Efficacy of Extended-Duration Transdermal Nicotine Therapy,'' *Clinical Pharmacology and Therapeutics,* 87(5):553–57, 2010.
19. Lindson, N. and Aveyard, P., ''An Updated Meta-Analysis of Nicotine Preloading for Smoking Cessation: Investigating Mediators of the Effect,'' *Psychopharmacology,* 214(3):579–92, 2011.
20. Murray, R.P., et al., ''Safety of Nicotine Polacrilex Gum Used by 3,094 Participants in the Lung Health Study. Lung Health Study Research Group,'' *CHEST,* 109(2):438–45, 1996.
21. Murray, R.P., et al., ''Does Nicotine Replacement Therapy Cause Cancer? Evidence From the Lung Health Study,'' *Nicotine & Tobacco Research,* 11(9):1076–82, 2009.
22. Newhouse, P., et al., ''Nicotine Treatment of Mild Cognitive Impairment: A 6-Month Double-Blind Pilot Clinical Trial,'' *Neurology,* 78(2):91–101, 2012.
23. Piper, M.E., et al., ''A Randomized Placebo-Controlled Clinical Trial of 5 Smoking Cessation Pharmacotherapies,'' *Archives of General Psychiatry,* 66(11):1253–62, 2009.
24. Rennard, S.I., et al., ''Efficacy of the Nicotine Inhaler in Smoking Reduction: A Double-Blind, Randomized Trial,'' *Nicotine & Tobacco Research,* 8(4):555–64, 2006.
25. Rose, J.E., et al., ''Mecamylamine Combined With Nicotine Skin Patch Facilitates Smoking Cessation Beyond Nicotine Patch Treatment Alone,'' *Clinical Pharmacology and Therapeutics,* 56(1):86–99, 1994.
26. Rose, J.E., et al., ''Nicotine-mecamylamine Treatment for Smoking Cessation: The Role of Precessation Therapy,'' *Experimental and Clinical Psychopharmacology,* 6(3):331–43, 1998.
27. Rose, J.E., et al., ''Precessation Treatment With Nicotine Skin Patch Facilitates Smoking Cessation,'' *Nicotine & Tobacco Research,* 8(1):89–101, 2006.
28. Rose, J.E., et al., ''Precessation Treatment With Nicotine Patch Significantly Increases Abstinence Rates Relative to Conventional Treatment,'' *Nicotine & Tobacco Research,* 11(9):1067–75, 2009.
29. Schuurmans, M.M., et al., ''Effect of Pretreatment With Nicotine Patch on Withdrawal Symptoms and Abstinence Rates in Smokers Subsequently Quitting With the Nicotine Patch: A Randomized Controlled Trial,'' *Addiction,* 99(5):634–40, 2004.
30. Tønnesen, P., et al., ''Higher Dosage Nicotine Patches Increase One-Year Smoking Cessation Rates: Results From the European CEASE Trial,'' *European Respiratory Journal,* 13(2):238–46, 1999.
31. Wang, D., et al., '' 'Cut Down to Quit' With Nicotine Replacement Therapies in Smoking Cessation: A Systematic Review of Effectiveness and Economic Analysis,'' *Health Technology Assessment,* 12(2):iii-iv, ix-xi, 1–135, 2008.
32. Wennike, P., et al., ''Smoking Reduction Promotes Smoking Cessation: Results From a Double Blind, Randomized, Placebo-Controlled Trial of Nicotine Gum With 2-Year Follow-Up,'' *Addiction,* 98(10):1395–402, 2003.
33. West, R., et al, ''A Comparison of the Abuse Liability and Dependence Potential of Nicotine Patch, Gum, Spray and Inhaler,'' *Psychopharmacology,* 149(3):198–202, 2000.
34. Zevin, S., et al, ''Dose-Related Cardiovascular and Endocrine Effects of Transdermal Nicotine,'' *Clinical Pharmacology and Therapeutics,* 64(1):87–95, 1998.

V. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at *http://www.regulations.gov*.

1. Centers for Disease Control and Prevention, ''Annual Smoking-Attributable Mortality, Years of Potential Life Lost, and Productivity Losses—United States, 2000–2004,'' *Morbidity and Mortality Weekly Report,* 57(45):1226–1228; November 14, 2008.
2. Centers for Disease Control and Prevention, ''Annual Smoking-Attributable Mortality, Years of Potential Life Lost, and Productivity Losses—United States, 1995–1999,'' *Morbidity and Mortality Weekly Report,* 51(14):300–303; April 12, 2002.
3. Centers for Disease Control and Prevention, ''Quitting Smoking Among Adults—United States, 2001–2010,'' [serial online], *Morbidity and Mortality Weekly Report,* 60(44):1513–1519; November 11, 2011.

Dated: March 26, 2013.

Peter Lurie,

Acting Associate Commissioner for Policy and Planning.

[FR Doc. 2013–07528 Filed 4–1–13; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Indian Health Service

Request For Public Comment: 60-Day Proposed Information Collection: Indian Health Service Medical Staff Credentials And Privileges Files

AGENCY: Indian Health Service, HHS.

ACTION: Notice.

SUMMARY: In compliance with Section 3506(c)(2)(A) of the Paperwork