Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of nicotine replacement therapy (NRT) drug products, including but not limited to those intended to help cigarette smokers stop smoking.[2] This guidance reflects the FDA's current recommendations regarding overall development programs to support NRT drug products for smoking cessation and related chronic indications.[3] FDA hosted a public hearing and published a notice in the *Federal Register* requesting comments on the Agency's approach to evaluating the safety and effectiveness of NRT drug products, including how the drug products should be used and labeled.[4] This draft guidance takes into consideration the feedback received and is intended to serve as a focus for continued discussions among the Agency, pharmaceutical sponsors, the academic community, and the public on this topic.[5]

[1] This guidance has been prepared by the Division of Anesthesia, Analgesia, and Addiction Products and the Division of Nonprescription Drug Products in the Center for Drug Evaluation and Research at the Food and Drug Administration, with the assistance of the Center for Devices and Radiological Health (CDRH) and the Office of Combination Products (OCP) at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *sponsor* includes any sponsor of an investigational new drug application or applicant for a new drug application or abbreviated new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act.

[3] As used in this guidance, the term *chronic indications* involves intermittent or continuous use resulting in 6 months or more exposure over a lifetime.

[4] See the *Federal Register* notice The Food and Drug Administration's Approach to Evaluating Nicotine Replacement Therapies; Public Hearing; Request for Comments, published on November 30, 2017 (82 FR 56759; Docket No. FDA-2017-N-6529).

[5] In addition to consulting guidances, sponsors are encouraged to contact the appropriate review division to discuss specific issues that arise during the development of NRT drug products.

This guidance focuses on drug development and trial design issues that are specific to the study of NRT drug products.[6]

Nonclinical studies can be needed to develop NRT drug products depending on specific aspects of the drug product, such as the route of administration, and the dose of excipients and impurities, including extractables and leachables. This guidance does not address recommendations for nonclinical development of NRT drug products. That topic can be addressed through feedback from the relevant FDA review division. Nonclinical development of an NRT drug product with an oral inhalation route of administration is addressed in the draft guidance for industry *Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products* (August 2018).[7]

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design that are not specific to development of NRT drug products. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001) and in the ICH draft guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (October 2017).[8]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

All existing FDA-approved NRT drug products (prescription and nonprescription) are approved for cessation of cigarette smoking. However, the Agency is committed to increasing access to and use of therapies, including NRT drug products, which could help more smokers quit.

NRT drug products are typically studied and labeled for use as adjuncts to behavioral self-help materials and to date have involved single treatment regimens that begin on the patient's *quit day*. However, other treatment regimens (e.g., pretreatment before quit day, quitting by gradual reduction (reduce to quit), using two NRT drug products together) could also be developed to help cigarette smokers quit. These alternate regimens are discussed further in section III., Development Program.

[6] For information on development programs for other drugs, biologics, or devices for smoking cessation and related indications, sponsors should contact the Division of Anesthesia, Analgesia, and Addiction Products, the Division of Nonprescription Drug Products, the Office of Device Evaluation in CDRH, or the Office of Cellular, Tissue, and Gene Therapies in the Center for Biologics Evaluation and Research.

[7] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[8] When final, this guidance will represent the FDA's current thinking on this topic.

NRT drug products can be developed for the following chronic indications:

- Smoking cessation
- Reduction in risk of relapse

NRT drug products that first have demonstrated effectiveness for smoking cessation or reduction in risk of relapse can also include additional information in labeling by demonstrating effectiveness in the following secondary endpoints:

- Reduction of urge to smoke and relief of cue-induced craving in former smokers
- Relief of withdrawal symptoms not associated with a cessation attempt

These indications are discussed further in section III., Development Program.

III. DEVELOPMENT PROGRAM

Both the regulatory pathway for an NRT drug product and the amount of nonclinical or clinical information needed to support approval can depend on the characteristics of the investigational NRT drug product relative to an approved NRT drug product.

The need for nonclinical studies to develop NRT drug products depends on specific aspects of the drug product, such as the excipients and impurity levels and the route of administration. The safety of chemicals derived from a delivery system, including extractable and leachable impurities from the container closure, should be addressed based on levels detected during stability testing and under the proposed conditions of use.[9] FDA encourages sponsors to consult the appropriate review division to discuss whether toxicity testing is recommended for their drug products.

In general, as discussed in section III.A., Recommended Studies and Application Type to Support Approval, an application for an NRT drug product that is *the same as* an approved product in many respects (including active ingredient, dosage form, strength, route of administration, and, with certain exceptions labeling) and bioequivalent to the approved product can be submitted as an abbreviated new drug application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). In addition, an application for an NRT in a new drug application (NDA) submitted pursuant to section 505(b)(2) of the FD&C Act may rely, in part, on FDA's findings of safety and effectiveness for an approved product, provided the application establishes that such reliance is scientifically appropriate (e.g., by demonstrating sufficiently similar bioavailability) and includes data to support any aspects of the proposed NRT product that represent modifications to the approved product relied upon. A 505(b)(2)

[9] The sponsor should consult the appropriate review division for feedback on a proposed nonclinical development plan. For more information on considerations for an NRT drug product with an oral inhalation route of administration, see the draft guidance for industry *Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products*. When final, this guidance will represent the FDA's current thinking on this topic.

application may or may not require clinical trials to establish safety or effectiveness, depending on the drug product's characteristics.[10] FDA anticipates that most sponsors will submit marketing applications for NRT drug products using one of these regulatory pathways.

Although the systemic effects of nicotine are well characterized, there are many sources of variability in the effectiveness of specific regimens and drug products. Therefore, in general, FDA recommends two adequate and well-controlled trials to demonstrate that an investigational NRT drug product with characteristics *different from* an approved NRT drug product is effective for smoking cessation or reduction in risk of relapse. For drug products that have different characteristics, an NDA under section 505(b)(2) of the FD&C Act or an NDA under section 505(b)(1) of the FD&C Act (containing full reports of investigations of safety and effectiveness that were conducted by or for the sponsor or for which the sponsor has a right of reference) can be necessary.

FDA considers tobacco dependence to be a serious or life-threatening condition. The Agency determines on a case-by-case basis whether an NRT drug product meets the criteria (e.g., significant improvement over existing therapies, address an unmet medical need) for inclusion in FDA's expedited development and review pathways.[11] FDA encourages a sponsor that believes its drug product represents a significant improvement over approved NRT drug products to consult FDA early in the development program to discuss whether the drug product may be eligible for review under one of the expedited pathways.

If the NRT drug product includes a device constituent part or parts to enable use of the drug product, FDA generally would regulate the drug product as a drug-device combination product with the Center for Drug Evaluation and Research (CDER) as the lead regulatory center.[12]

[10] Under these abbreviated approval pathways, in general, a sponsor can rely on FDA's finding of safety and effectiveness for a drug product approved under section 505(c) of the FD&C Act to the extent the products share characteristics.

[11] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014).

[12] The term *combination product* is defined at 21 CFR 3.2. A combination product is comprised of any combination of a drug, device, and biological product "constituent parts." See 21 CFR 4.3. The center with primary jurisdiction (the lead) for premarket review and regulation of a combination product is assigned based on which constituent part provides the combination product's primary mode of action (PMOA) (i.e., makes the greatest contribution to the combination product's overall intended therapeutic effect (see 21 USC 353(g)(1)(C), 21 CFR 3.2)). For example, an NRT combination product composed of a drug product and of a device that serves to deliver the drug product would have a drug PMOA, and CDER would have the lead for the combination product's regulation. Examples of such NRT combination products would include transdermal patches and e-cigarettes containing or copackaged with a drug. For such combination products, in general, CDER will be the point of contact and will coordinate with CDRH as well as OCP as appropriate to ensure utilization of relevant expertise and consistency of regulatory treatment. OCP is also available to assist sponsors, as needed, in identifying appropriate contact points (including those in the lead center), resolving substantive issues, or otherwise facilitating interactions with the Agency and collaboration among Agency components.

Sponsors should address issues related to the device constituents to establish the safety and effectiveness of the drug-device combination product as a whole.[13]

A. Recommended Studies and Application Type to Support Approval

Sponsors developing NRT drug products should consider the following regarding recommended studies and types of drug applications.

1. Investigational NRT Drug Products That Rely on an Approved NRT Drug Product

a. Generic versions of approved NRT drug products

For an investigational NRT smoking cessation drug product that has the same active ingredient, dosage form, strength, route of administration, and, with certain exceptions, labeling as an approved reference NRT drug product, comparative bioavailability pharmacokinetic (PK) studies can be conducted to confirm that the investigational NRT drug product is bioequivalent to the approved reference listed NRT drug product. For these drug products, provided they are bioequivalent, FDA believes that additional clinical efficacy trials are not needed if the investigational drug product does not claim any additional benefit or superiority over the reference drug product. The sponsor should submit an ANDA to support approval of such a drug product.[14]

For drug products for smoking cessation that otherwise would meet the requirements for an ANDA relying on an approved NRT drug product but are intended to have advantages over approved NRT drug products, as expected for designation for expedited development programs (e.g., superior effectiveness, improved safety), sponsors should demonstrate these improvements in head-to-head clinical trials. In general, demonstrating shorter time to maximum plasma concentration (*more rapid PK*), alone, is not sufficient to qualify the drug product for expedited development programs. The sponsor can submit a 505(b)(2) NDA to support approval of such a drug product.[15]

[13] For example, delivery device constituent parts should be shown to be compatible for use with the final formulation of the drug constituent part through appropriate studies, including extractable and leachable studies, performance testing, and stability studies. In addition, in vitro performance testing data may be needed to support the delivery device constituent part of the proposed combination product and design validation of the combination product. For additional guidance and information regarding regulatory considerations for combination products, see the Office of Combination Products web page at https://www.fda.gov/CombinationProducts/default.htm.

[14] FDA encourages sponsors that intend to submit an ANDA to consult FDA's product-specific guidances for demonstrating bioequivalence for generic nicotine-containing drug products for additional information. Check the FDA guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[15] Sponsors should note that an approved product will not receive 3-year exclusivity for bioavailability studies. See section 505(c)(3)(E)(iii) of the FD&C Act and 21 CFR 314.108.

b. Drug product modifications that alter the mode of administration

Certain NRT drug products may have the same route of administration (e.g., oral), but the drug products may differ in the method an individual uses to extract the nicotine (e.g., swallowing versus dissolving on the tongue). For purposes of reviewing these drug products, FDA will refer to these drug products as having different modes of administration. For example, a proposed different mode of administration for an NRT gum product for smoking cessation could involve a new[16] method of user extraction, such as instructing users to chew the gum product as a conventional gum (swallowing the liquid), instead of instructing users to repeat a process of chewing and then placing the piece of gum product between their cheek and gums, as is set forth in the labeling for currently approved NRT gum products for smoking cessation. Other examples of an NRT drug product's mode of administration (which could also affect the route of administration or dosage form) could include chewing, dissolving in mouth, spraying into mouth, inhaling, swallowing, applying to the skin, swishing, placing on buccal mucosa.

For sponsors seeking approval for a drug product that alters the mode of administration compared to an approved NRT drug product, sponsors can rely on a previous Agency finding of systemic safety for the reference NRT drug product, provided that the application establishes that such reliance is scientifically appropriate (e.g., confirm via PK studies that the investigational NRT drug product provides sufficiently similar venous plasma levels of nicotine). The Agency anticipates that no efficacy trials would be needed for these types of NRT drug products and that sponsors would be able to submit a 505(b)(2) NDA.

c. Different instructions for use

If the investigational NRT smoking cessation drug product is similar to an approved NRT drug product, but the sponsor proposes instructions for use that are different from the reference NRT drug product (e.g., instructions for a new use regimen for achieving smoking cessation), the Agency anticipates that the sponsor would need to submit either a 505(b)(2) NDA or a full 505(b)(1) NDA. FDA would expect the sponsor to conduct a PK study and one or more clinical efficacy trials. For example, in cases where the investigational NRT drug product's active ingredient and route of administration are otherwise the same as those of an approved NRT drug product, but the drug product proposes a different treatment regimen (e.g., quitting by gradual reduction), a single adequate and well-controlled efficacy trial and appropriate PK bridging studies may suffice.[17] For a proposed over-the-counter (OTC) NRT drug product, in addition to the other investigations that would be necessary to demonstrate effectiveness in the prescription setting, the development program should include an actual-use efficacy trial (see section III.C.2., Sequential Approach for Development of OTC Drug Products). As discussed below, for these OTC NRT drug products, FDA recommends an incremental approach leading up to the actual-use efficacy trial.

[16] As used in this guidance, the term *new* is used when describing drug product characteristics that FDA has not previously approved for an NRT drug product.

[17] In limited cases where a sponsor demonstrates an NRT drug product's bioequivalence to an approved NRT drug product with a very similar dosage form using the intended dosing regimen, FDA may not require efficacy studies.

205 *2. NRT Drug Products That Are Significantly Different from Approved NRT Drug*
206 *Products*
207
208 a. New route of administration
209
210 For investigational NRT drug products that introduce a new route of administration, FDA
211 anticipates that more than one adequate and well-controlled clinical trial could be needed to
212 characterize the relationship of venous plasma levels and smoking cessation effectiveness
213 because the PK profile is likely to be substantially different from approved NRT drug products
214 and effectiveness cannot be predicted.[18] FDA anticipates that sponsors of drug products with a
215 new route of administration would need to submit a 505(b)(2) NDA or a full 505(b)(1) NDA.
216
217 b. New indication
218
219 Currently, all approved NRT drug products are indicated as aids to smoking cessation. Some
220 NRT drug products could also demonstrate effectiveness for reduction in risk of relapse in
221 former smokers.
222
223 Sponsors of approved NRT drug products (i.e., approved for smoking cessation) that seek to add
224 a reduction in risk of relapse indication should conduct one clinical efficacy trial in a population
225 of recent quitters (i.e., smokers who have quit within the past month). The data supporting the
226 drug product's previous approval as a cessation treatment can serve as confirmatory evidence of
227 the drug product's effectiveness.[19] These sponsors can submit an efficacy supplement for
228 approval of the new indication. See section III.C.5.a., Reduction in risk of relapse, for discussion
229 of primary endpoints.
230
231 A sponsor seeking an indication for reduction in risk of relapse for a new (not previously
232 approved for smoking cessation) NRT drug product should conduct two clinical efficacy trials in
233 a population of recent quitters. FDA is likely to require that drug products proposing such a new
234 indication submit a 505(b)(2) NDA or a full 505(b)(1) NDA.
235
236 *3. Secondary Endpoints*
237
238 Sponsors can also seek to include information about secondary endpoints in the NRT drug
239 product's labeling for a drug product that has already demonstrated effectiveness in cessation or
240 reduction in risk of relapse. Such secondary endpoints could include a reduction in the urge to

[18] For additional guidance on the nonclinical safety information that FDA expects to be necessary to support the development of orally inhaled nicotine-containing drug products, see the draft guidance for industry *Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products*. When final, this guidance will represent the FDA's current thinking on this topic.

[19] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998).

smoke or relief of cue-induced craving in former smokers, using patient-reported outcome (PRO) instruments adequately developed for this purpose.[20]

It is understood that the mechanism of action by which NRT drug products help smokers to quit smoking is via the amelioration of acute symptoms of nicotine withdrawal, including nicotine craving associated with quitting smoking. Drug products that have demonstrated effectiveness as an aid to smoking cessation are also labeled for relief of withdrawal symptoms in patients *who are trying to quit smoking*. Additionally, a sponsor that can demonstrate, as a secondary endpoint, that the drug product provides relief of withdrawal symptoms in smokers *who are not trying to quit smoking*, may be able to include labeling instructions to cover situations in which such individuals are required to abstain and experience withdrawal (e.g., while traveling on an airplane). Given the current lack of scientific consensus on how to establish a clinically relevant effect on withdrawal symptoms alone, FDA does not envision that relief of withdrawal symptoms would be granted as a stand-alone indication for an NRT drug product that has not been shown to be effective as an aid to smoking cessation.

FDA expects that a sponsor evaluating secondary endpoints for an NRT drug product could demonstrate effectiveness in a single clinical trial. The trial's sample size should be large enough to provide sufficient power to show a treatment effect on the secondary endpoints.[21] A sponsor seeking to include information about secondary endpoints in the labeling of an approved NRT drug product will need to submit an efficacy supplement to the NDA with supporting data as described in section III.C.5., Other Efficacy Endpoints.

B. General Considerations: Early Phase Clinical Development

In the phase 1 program, the sponsor should enroll healthy nicotine-experienced adults (typically, current smokers) and characterize the PK profile of the drug product and any sources of variability (e.g., user technique) to provide information to determine the recommended dose, interdose interval, instructions for use, etc. This part of the program should usually compare the pharmacokinetics of the drug product to that of an approved NRT drug product. For some drug products, the phase 1 program may include bioavailability comparisons to more than one approved drug product. In certain cases, when the PK profile for the investigational NRT drug product falls between the profiles for two approved NRT products, the sponsor can apply a *bracketing* strategy. Using this approach, the application may rely in part on the Agency's previous finding of systemic safety for the *higher* nicotine exposure drug product and, in part, on the Agency's previous finding of effectiveness for the *lower* nicotine exposure drug product. FDA notes that the sponsor's ability to use the bracketing approach depends on the shape of the PK curve and the similarity of the drug products being bracketed.

[20] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

[21] Sponsors should consult the draft guidance for industry *Multiple Endpoints in Clinical Trials* (January 2017) for guidance on designing a clinical trial that is sufficiently powered to evaluate secondary endpoints. When final, this guidance will represent the FDA's current thinking on this topic.

Early phase clinical development for NRT drug products should characterize drug activity for a range of nicotine doses. Dose-ranging studies are generally performed in phase 2 trials. The sponsor should characterize the investigational NRT drug product's pharmacokinetics and toxicity in a broad population of smokers, without excluding those with comorbidities and those at higher risk of experiencing adverse events (e.g., smokers with hepatic, renal, pulmonary, or other organ impairment, smokers on certain psychiatric medications). If the information is not available by reference to other approved drug products or literature, drug-drug interaction studies may be needed to assess the safety of concomitant use with medications commonly used in the target population, including other smoking cessation medications. Specific safety studies related to the route of administration (e.g., dermal sensitization, oral mucosal safety, effect of high-pH or low-pH beverages), expected duration of therapy, or drug product novelty may also be needed for some NRT drug products.

If sponsors attempt to *reverse engineer* a dose and dosing regimen that suggests bioequivalence to an approved regimen, the regimen should be realistic and related to the duration of action of the investigational drug product. If not, users are unlikely to follow the instructions.

C. General Considerations: Efficacy Trials

For applications requiring an efficacy trial, consider the following:

1. General Efficacy Trial Design for All NRT Drug Products

The sponsor should compare the investigational NRT drug product to placebo in a randomized, double-blind, superiority trial design. The placebo should be indistinguishable from the investigational NRT drug product in all relevant aspects (appearance, taste, texture, etc.). For NDAs for drug products intended to be advancements or improvements over existing therapy (as discussed in section III.A.1.a., Generic versions of approved NRT drug products), sponsors may be able to use an approved NRT drug product as the active comparator in the head-to-head trial demonstrating superiority to active control, if there are no outstanding questions about the safety of the investigational NRT drug product. If questions remain about the safety of the investigational NRT drug product, the trial design should also include a placebo control.

Subjects should be randomized to treatment with the investigational NRT drug product or control(s). Sponsors should document a rationale for the number of doses and regimens being studied, to address the various populations of smokers. If the intent is that smokers will use the drug product for a longer term (e.g., for reduction in risk of relapse), sponsors should test more than one dose and document a justification for each dosage level. Enrollment may be stratified based on the number of previous quit attempts, the number of cigarettes used per day, or the severity of dependence to ensure representation across categories. For adult subjects, measures such as baseline scores on the Fagerstrom Test of Nicotine Dependence or the *time-to-first-cigarette* method can be used for treatment allocation when stratifying by severity of dependence. Trial visits should occur at approximately weekly intervals for monitoring of adverse events and collection of efficacy data.

At efficacy ascertainment visits, the subject should be queried about any smoking since the last trial visit, and biological markers of smoking or tobacco exposure should be collected. At a minimum, exhaled breath carbon monoxide (CO) should be assessed. FDA encourages incorporation of other markers that can differentiate exposure to tobacco from exposure to NRT drug products. For investigational NRT drug products with novel delivery systems, it may be necessary to demonstrate that customary tests such as exhaled CO are unaffected by use of the drug product and/or placebo.

2. Sequential Approach for Development of OTC Drug Products

Sponsors developing an OTC drug product should bear in mind that it is often not possible to answer all regulatory questions in a single trial. Therefore, the development program for these NRT drug products may include several trials to identify and refine the proper dosing regimen and self-help materials before undertaking the real-world or actual-use trial that would support approval.

The sponsor should develop a label that it believes may be close to the to-be-marketed Drug Facts label and test that label in a label comprehension study. The label comprehension testing process should be iterative and should lead to the development of the best understood label.[22] If the drug product has instructions for use, these should be tested in a human factors study to demonstrate that consumers can understand the instructions on how to use the drug product.[23]

Label comprehension and human factors studies are necessary at the early stages of development because if the NRT drug product package (e.g., product/regimen, self-help materials) does not perform as expected, the source of failure may be difficult to determine. Furthermore, subsequent changes to the drug product may require retesting in additional clinical trials.

Sponsors should then provide clinical trial subjects with a package containing the NRT drug product with the planned Drug Facts label, along with any instructions or self-help materials that are intended to be marketed with the drug product. An efficacy trial that features assistance from trial staff to ensure that the subjects follow directions on the label provides evidence that the drug product, when properly used, is effective. However, at least one efficacy trial should involve an *all-comers* population where no training and education on how to use the drug product is provided by the clinical trial staff. This real-world or actual-use trial is intended to provide evidence that consumers can use the drug product effectively and safely based on the label without assistance.

In general, it is desirable that the OTC development program proceeds in the following incremental and sequential fashion: formative label comprehension study; formative human factors study (if relevant); clinical trial with training/education from trial staff; pivotal label comprehension and human factors studies with the refined labeling utilizing clinical trial results;

[22] See the guidance for industry *Label Comprehension Studies for Nonprescription Drug Products* (August 2010).

[23] Regarding NRT combination products, see the draft guidance for industry and FDA staff *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016). When final, this guidance will reflect FDA's current thinking on this topic.

actual-use trial with no training or education from trial staff. One or more self-selection studies may also be necessary at some point in development to evaluate if the drug product use would be limited to the intended population (such as those looking to quit smoking, rather than nonsmokers) and/or to populations for whom a drug product would not be contraindicated.[24] Note that depending on the particulars of the drug product, the sponsor may be able to incorporate a self-selection component into a real-world or actual-use trial.

3. Study Population

In general, phase 3 clinical trials for an NRT drug product indicated for smoking cessation should study active smokers 18 years of age and older who wish to quit smoking, including subjects with comorbidities similar to those of the target population for the NRT drug product. In some circumstances, sponsors can consider requiring that subjects use a certain minimum number of cigarettes per day. This may be the case, for example, if an investigational NRT drug product provides a nicotine dose that exceeds the nicotine delivered by *light* smoking (i.e., smoking 10 or fewer cigarettes per day). Efficacy trials for certain indications may need a population of recent quitters, regardless of the method used. For discussion of studies in pediatric populations, see section III.D.1., Pediatric Populations.

4. Cessation Efficacy Endpoints

The endpoint for a smoking cessation trial is the proportion of subjects who are abstinent from cigarette use over the entire efficacy ascertainment period.[25] A trial is considered to demonstrate effectiveness if significantly more subjects achieve abstinence when treated with the investigational NRT drug product as compared to subjects treated with the placebo. However, FDA will take the size of the effect into consideration during its benefit-risk assessment.

In general, *abstinence* is defined as no cigarette use over the entire course of the efficacy ascertainment period by subject self-report and biological verification at intervals of approximately 1 to 2 weeks. A longer interval between self-reporting and verification visits may be acceptable in some instances (e.g., trials that are more than 3 months long). For trials with longer efficacy ascertainment periods of 6 or 12 months, sponsors can consider defining abstinence to incorporate a maximum allowable number of cigarettes.[26] The efficacy ascertainment period generally runs from the first day of treatment to the last day of treatment. The duration of the efficacy ascertainment period should be sufficient to justify the intended duration of treatment. Thus, an investigational NRT drug product that a sponsor intends to label as a 6-month course of treatment should be supported by 6 months of documented abstinence. If the effect of the treatment is not expected to result immediately upon initiation of the drug product because of the mechanism of action, pharmacokinetics, or other factors, then efficacy

[24] See the guidance for industry *Self-Selection Studies for Nonprescription Drug Products* (April 2013).

[25] Note that the sponsor can allow for a grace period before the beginning of the efficacy ascertainment period. Subjects that have *slips* during the grace period would not be adjudicated as nonquitters.

[26] See, for example, the Russell Standard as described in Robert West et al., 2005, "Outcome Criteria in Smoking Cessation Trials: Proposal for a Common Standard," *Addiction*, 100(3):299–303.

ascertainment can take place over a period that begins after a protocol-specified *grace period*. The sponsor should justify the duration of any such grace period.

FDA considers 4 weeks to be the absolute minimum period of efficacy ascertainment. The proportion of subjects abstaining for less than 4 weeks is not considered informative because such short periods of abstinence are not known to confer health benefits. Similarly, a *floating* period of efficacy ascertainment (e.g., any 4 consecutive weeks) is not considered informative because subjects who relapse while still on treatment cannot be viewed as successful quitters.

5. Other Efficacy Endpoints

a. Reduction in risk of relapse

Sponsors seeking a reduction in risk of relapse indication should provide evidence from clinical trials showing that recent quitters (i.e., smokers who have quit within the past month), regardless of the method used, even without the use of NRT or other medications (cold turkey), can benefit from a course of treatment with the NRT drug product to reduce the risk of relapse. The clinical trials intended to support this maintenance indication should have the definition of relapse prespecified in the protocol, an ascertainment window, at a minimum, of 6 months to 1 year, and use the proportion of trial subjects not relapsing as the primary endpoint.[27]

These clinical trials could have a double-blind, placebo-controlled design in which recent quitters are randomized to treatment or placebo, then followed for the efficacy ascertainment period for evaluation of relapse. Alternatively, a randomized withdrawal design can be employed, in which responders to an open label period of treatment with the drug product are randomized to continue on the drug product or to blindly switch to a matching placebo, then followed for the efficacy ascertainment period for evaluation of relapse.

b. Reduction in urge to smoke and relief of cue-induced craving in former smokers

Former smokers, even those with a long period of successful abstinence from smoking, can have episodes in which they experience uncomfortable feelings of a desire to smoke. These episodes may be provoked by circumstances or cues that have been previously associated with smoking. Even in successful abstainers at low risk for relapse, the experience of these provoked urges or cravings are unpleasant and can be a target for treatment.

Drug products that have already demonstrated effectiveness in smoking cessation or reduction in risk of relapse may be able to include information in labeling about effectiveness in relieving the urge to smoke and cue-induced cravings in populations of former smokers based on suitable trials.

[27] Id. For example, sponsors may consider a study design where treatment success is defined as smoking no more than five cigarettes during the efficacy ascertainment period.

Sponsors should identify or develop fit-for-purpose PRO instruments and recruit former smokers who report experiencing urges or cravings and who are interested in finding ways to relieve this symptom.[28]

c. Relief of withdrawal symptoms not associated with a cessation attempt

Drug products that have already demonstrated effectiveness in smoking cessation or reduction in risk of relapse may be able to include information in labeling about effectiveness in relieving withdrawal symptoms not associated with a cessation attempt. Sponsors seeking to establish their NRT drug products' effectiveness in relieving withdrawal symptoms not associated with a cessation attempt can demonstrate this effect in behavioral pharmacology laboratory studies using suitably designed PRO instruments.[29]

6. New Regimens for Cessation and Reduction in Risk of Relapse

NRT drug products can be used in a variety of ways to achieve smoking cessation or to reduce the risk of relapse. FDA considers these to be treatment regimens, not separate indications. Any treatment regimen that the sponsor believes may be effective for smoking cessation or reduction in risk of relapse can be evaluated in randomized, double-blind trials of the design described above. This includes regimens in which subjects gradually reduce their smoking over time while using the drug product (i.e., reduce to quit) and regimens in which the drug product is introduced before the subject's planned quit day (i.e., pretreatment), or other regimens the sponsor may wish to study. In each case, the design and endpoints are as described above.

The sponsor should give careful attention to providing clear instructions to trial subjects on how to follow new regimens. Phase 2 initial trials and label comprehension studies (for OTC drug products) of the appropriateness of the instructions are likely to be needed.

Clinical trials to demonstrate the effectiveness of a particular combination of NRT drug products should employ randomized, double-blind, double-dummy, factorial design. The contribution of each component to the effectiveness should be demonstrated.[30] The design and endpoints for such trials are as described above. Sponsors should evaluate the optimal dose combinations in phase 2 trials before undertaking definitive trials.

[28] For additional guidance on selecting endpoints, see the draft guidance for industry *Multiple Endpoints in Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic. For additional guidance on developing validated PRO instruments, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

[29] For guidance on development of measures for assessing PROs, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

[30] For additional information on demonstrating the contribution of each of the drug product's components to effectiveness, see 21 CFR 300.50 and the proposed rule Fixed Combination and Co-Packaged Drugs: Applications for Approval and Combinations of Active Ingredients Under Consideration for Inclusion in an Over-the-Counter Monograph, published on December 23, 2015 (80 FR 79776).

As described above in section III.C.2, Sequential Approach for Development of OTC Drug Products, drug products with alternative regimens being developed for OTC use should demonstrate effectiveness of the alternative regimen in an actual-use efficacy trial.

Sponsors interested in studying new NRT regimens (for prescription or OTC use) or combination of NRT drug products for smoking cessation should contact the CDER Division of Anesthesia, Analgesia, and Addiction Products or the Division of Nonprescription Drug Products, and the Office of Device Evaluation in the Center for Devices and Radiological Health, as appropriate, to discuss the development plan for the drug product.

D. Other Considerations

1. Pediatric Populations

To comply with the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c),[31] an NDA for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indication(s) to support dosing and administration in all pediatric subpopulations unless the requirement is waived or deferred. The sponsor must submit an initial pediatric study plan (iPSP) outlining the studies it plans to conduct in the pediatric population and addressing any plans for waiver, partial waiver, or deferral requests of PREA-required trials no later than 60 days after the end-of-phase 2 meeting, unless FDA and the sponsor agree upon another submission date. Sponsors should consult the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (March 2016).[32]

The iPSP for NRT drug products for smoking cessation or related indications should include an up-to-date estimate of the size of the pediatric smoking population, the use of NRT drug products and smoking cessation services by adolescents, and the feasibility of conducting clinical studies with the NRT drug product in the pediatric population.[33] Given that use of tobacco products frequently starts in early adolescence, drug products approved for smoking cessation have the potential to benefit and be used in the pediatric population. Based on the current prevalence of smoking in younger children, the Agency has waived the PREA requirements for clinical studies of NRT drug products in patients younger than 12 years of age because clinical studies would be highly impracticable in that age group. However, the Agency's thinking may change, and any request for waiver of clinical studies in any specific pediatric age group should include appropriate justification(s). If the Agency determines that studies are highly impracticable in pediatric patients 12 years of age and older, or data are submitted that support a different waiver criterion under PREA, the Agency may also grant a waiver of PREA studies in this population.

[31] See PREA (Public Law 108-155; section 505B of the FD&C Act; 21 U.S.C. 355c).

[32] When final, this guidance will represent the FDA's current thinking on this topic.

[33] For additional guidance on PREA requirements, see the draft guidance for industry *How to Comply with the Pediatric Research Equity Act* (September 2005). When final, this guidance will represent the FDA's current thinking on this topic.

Efficacy data from adult subjects cannot be extrapolated to pediatric patients because of differences, such as patterns of tobacco use and nicotine dependence, between adult and pediatric smokers. Thus, if a pediatric assessment in a pediatric population is required, effectiveness should be established in the relevant pediatric age cohort. Dose selection in pediatric patients should be based on adolescent PK data, and any PRO instruments should be fit-for-purpose in the adolescent population.

PREA-required studies are based on the indication(s) approved or sought in adults. Interested sponsors may also submit a proposed pediatric study request for the Agency to issue a written request for pediatric data for pediatric studies under the Best Pharmaceuticals for Children Act as described in section 505A(d)(1)(A) of the FD&C Act; 21 U.S.C. 355a(d)(1)(A).

2. Behavioral Counseling

Behavioral counseling, if provided, should be standardized. In addition, for pediatric patients, behavioral counseling should be developmentally appropriate and intended for this pediatric population. For a prescription medication, the counseling provided should be feasible for delivery in a typical primary care setting. Behavioral counseling can be provided at trial visits, but the sponsor should define behavioral counseling in the protocol, and it should be standardized across sites. If more complex or extensive behavioral programs are included, the sponsor can consider marketing the drug product as an adjunct to the specific behavioral treatment studied. If behavioral counseling is provided in conjunction with a drug product intended for OTC marketing, the behavioral counseling should be in a self-help format that can be marketed with the drug product.

3. Statistical Considerations

a. Analysis populations

Subjects who were exposed to any treatment, including those who received only self-help materials, and discontinued the trial without post baseline efficacy evaluations should be included in the intent-to-treat population as nonresponders (continuing smokers) for the primary endpoint. The protocol should clearly describe the primary estimand of interest.

The safety population should include all randomized subjects who received at least one dose of the investigational NRT drug product and were evaluated for any on-treatment safety information. Subjects who did not return for any on-treatment evaluations should be excluded from the denominator for the purposes of calculating rates of adverse events.

b. Missing efficacy data

The protocol should explain how missing data will be addressed relative to the primary estimand and describe the plan for imputation of smoking status information for subjects with intermittent missing data. Generally, in a trial with closely spaced efficacy ascertainment visits, the sponsor can consider a subject abstinent for a single missing visit if the subject had documented confirmed abstinence before and after the missing visit and self-reports abstinence at the time of

the missing visit. The sponsor should consider the subject nonabstinent if the subject misses two or more visits during the efficacy ascertainment period, if data for the subject are missing at the end of the period or if the subject withdraws from the trial before the end of the efficacy ascertainment period, regardless of smoking status at the time of withdrawal.

4. Clinical Benefit of Smoking Cessation

Quitting smoking can lower a person's chances of having lung disease and heart disease and of getting certain types of cancer that are related to smoking. For NRT drug products that have demonstrated effectiveness for cessation or reduction in risk of relapse, sponsors do not need to provide additional data to include information in the labeling about these therapeutic benefits of smoking cessation or maintaining abstinence from cigarettes.