

Draft Guidance on Selegiline

February 2026

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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.

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| Active Ingredient: | Selegiline |
| Dosage Form: | Film, extended release |
| Route: | Transdermal |
| Strengths: | 6 mg/24 hr, 9 mg/24 hr, 12 mg/24 hr |
| Recommended Studies: | One in vivo bioequivalence study with pharmacokinetic endpoints, one in vivo adhesion study, and one in vivo skin irritation study |
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1. Type of study: Bioequivalence study with pharmacokinetic endpoints
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 6 mg/24 hr
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments:
 - a. In this document, this dosage form is referred to as a transdermal delivery system (TDS) and includes products that may be described elsewhere or known as *patches, systems, or extended release films*.
 - b. Unless otherwise justified, the selegiline TDS should be applied to the same anatomical site on all subjects, selected from among those recommended in the approved labeling for the reference listed drug (RLD), and worn for 24 hours. Applicants should randomize subjects to receive either drug product TDS in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body.

- c. Contact of the TDS with the skin is essential for the in vivo performance of the TDS, and the pharmacokinetics may be altered when a TDS loses its adherence to the skin. Therefore, the adhesion of each TDS should be monitored and recorded throughout the bioequivalence study with pharmacokinetic endpoints. The applicant should prespecify their inclusion criteria for the statistical analysis of pharmacokinetic endpoints and perform their primary pharmacokinetic analysis on the per protocol population; however, samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS and regardless of the inclusion criteria for the statistical analysis of pharmacokinetic endpoints. Provisions should be included in the study protocol to ensure that deliberate actions with the intent to re-apply a detached area of the TDS, to apply pressure to the TDS, or to reinforce TDS adhesion with the skin (e.g., overlays) are avoided throughout the study.
- d. The applicant should refer to the most recent version of the guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*^a for the design and conduct of the bioequivalence study with pharmacokinetic endpoints.

Analyte to measure: Selegiline in plasma

Bioequivalence based on (90% CI): Selegiline

Waiver request of in vivo testing: The 9 mg/24 hr and 12 mg/24 hr strengths of the TDS may be considered for a waiver of in vivo bioequivalence testing based on (i) an acceptable bioequivalence study with the 6 mg/24 hr strength, (ii) acceptable comparative in vitro drug release testing between additional strengths and the 6 mg/24 hr strength using 12 dosage units per strength, and (iii) proportional similarity of the TDS formulation across all strengths.

The proportional similarity of the TDS formulation across all strengths means (i) that the amounts of active and inactive ingredients per unit of active surface area are identical across the different strengths of the test product, and (ii) that the ratios of the active surface areas of each strength of the test product compared to the 6 mg/24 hr strength of the test product are the same as the corresponding ratios for the active surface areas of each strength of the RLD compared to the 6 mg/24 hr strength of the RLD.

In vitro drug release method and sampling times: In vitro release should be included for quality control and to support waiver request of in vivo testing of additional strength(s). Provide an in vitro release method development report for the test product containing information and data that demonstrate the appropriateness of the selected in vitro release method¹ and sampling times, such as the discriminating ability to detect changes in critical quality attributes that could potentially impact drug product performance.

¹ Applicant-developed, United States Pharmacopeia (USP) drug product monograph, or Dissolution Methods database, <https://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>

2. Type of study: Adhesion study
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 6 mg/24 hr
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments:
- The applicant may elect to evaluate the bioequivalence (study 1) and the adhesion (study 2) in a single study with a combined purpose, or in independent studies. In either case, the studies should be adequately powered to evaluate the bioequivalence, and independently, the comparative assessment of adhesion.
 - The applicant should refer to the most recent version of the guidance for industry *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs*^a for the design and conduct of the independent adhesion study or the combined study to evaluate both bioequivalence and adhesion.
3. Type of study: Skin irritation study
Design: Randomized, evaluator-blinded, within-subject repeat design in vivo
Strength: 6 mg/24 hr (administered as one-half of the test articles)
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments:
- All test articles (i.e., one-half of the 6 mg/24 hr strength of both drug product TDS², optional vehicle TDS³, and optional negative control⁴) should be applied simultaneously to each subject at different positions on the same anatomical site recommended in the approved labeling of the RLD.
 - Sequential TDS applications of each test article should be made to the same position every 24 hours for a total of 21 consecutive days.
 - When evaluating the irritation potential only, applicants should compare the test articles in a minimum of 40 evaluable subjects, or a sufficient number of subjects to power the study at a level of 0.80 or higher, whichever is greater.
 - If the test product contains an inactive ingredient that is not present in the RLD and is known to be sensitizing, or at a higher amount/concentration than previously used in an FDA-approved drug product with a similar context of use, FDA recommends conducting a combined irritation and sensitization study. FDA encourages applicants who have questions related to the need for a sensitization study for a proposed product (with a proposed formulation composition) to seek feedback through a controlled correspondence or product development meeting.⁵

² The test product evaluated should be the actual product to be marketed.

³ The optional vehicle TDS should contain all of the inactive ingredients in the test product and be identical to the test product in every manner except for the absence of the inactive ingredient.

⁴ An example of the optional negative control treatment is an occlusive cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.

⁵ Applicants should refer to the most recent version of the guidance for industry *Controlled Correspondence Related to Generic Drug Development* and the most recent version of the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* for additional information describing the procedures on how to clarify regulatory expectations regarding the applicants' individual drug development program.

- e. Since the RLD has a matrix design that can be safely cut, the test product is anticipated to have a design that can also be safely cut to a smaller size. If the test product also has a design that can be safely cut to a smaller size, it should also be cut in half. It would not be acceptable to manufacture a separate batch of the test product in order to use a smaller TDS in this study.
- f. The applicant should refer to the most recent version of the guidance for industry *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs*^a for the design and conduct of the skin irritation (and sensitization) study.

Additional comments relating to all studies:

In addition to the recommendations in the general guidances referenced above, and the product specific recommendations related to the individual studies, the following product specific recommendations should be considered.

1. Exclusion criteria (the applicant may add additional criteria):
 - a. Psychiatric illness requiring treatment
 - b. History of pheochromocytoma
 - c. Taking selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline, and paroxetine); serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine and duloxetine); the tricyclic antidepressants clomipramine and imipramine, the opiate analgesics meperidine, tramadol, methadone, pentazocine, and propoxyphene; and the antitussive agent dextromethorphan
 - d. Taking buspirone, amphetamines, or cold products or weight-reducing preparations that contain sympathomimetic amines (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine)
2. Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
 - a. Amphetamines
 - b. Buspirone (anti-anxiety agent)
 - c. Carbamazepine (antiepileptic)
 - d. Bupropion hydrochloride
 - e. Cyclobenzaprine (relieves muscle spasm)
 - f. Decongestants
 - g. Dextromethorphan (cough suppressant)
 - h. Dual serotonin and norepinephrine inhibitors (e.g., desvenlafaxine, duloxetine, venlafaxine)
 - i. Monoamine oxidase inhibitors other than the drug product TDS (e.g., isocarboxazid, oral selegiline, rasagiline, phenelzine, tranylcypromine)
 - j. Methylphenidates (e.g., dexamethylphenidate, methylphenidate)
 - k. Narcotics and certain analgesics (e.g., cocaine, meperidine, methadone, pentazocine, propoxyphene, tramadol)
 - l. Oxcarbazepine (antiepileptic)

- m. Sympathomimetic amines (albuterol and metaproterenol (bronchodilators), midodrine (orthostatic hypotension))
 - n. Tetracyclic antidepressants (e.g., mirtazapine)
 - o. St. John's wort
 - p. Tyramine containing over-the-counter supplements
3. Provide a listing of foods and beverages that may cause adverse interactions with selegiline and should be avoided during the study, such as:
 - a. Foods that have a high tyramine content, such as aged cheeses, fava or broad bean pods, sauerkraut, soybean products, soy sauce, tofu, yeast extract, pickled herring, air dried, aged and fermented meats, sausages and salamis (e.g., cacciatore, hard salami, mortadella and pepperoni)
 - b. All varieties of tap beer and beers that have not been pasteurized so as to allow for ongoing fermentation
 4. Subjects should be advised that the use of alcohol is not recommended while taking the study drug.
 5. Blood pressure should be assessed at each visit.

Additional information:

Device:

The RLD is presented as a TDS. The TDS is the drug-device combination product.

FDA recommends that prospective applicants examine the critical design attributes of the RLD device when designing the test device.

User interface assessment:

An abbreviated new drug application for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.^a

Document History: Recommended August 2009; Revised October 2011, October 2016, October 2018, November 2019, February 2026

Unique Agency Identifier: PSG_021336

^a For the most recent version of a guidance, refer to the FDA guidance website at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.