



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2016-D-0785]

General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a guidance for industry entitled “General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products.” This guidance is intended to assist a person who plans to develop and submit an abbreviated new drug application (ANDA) to seek approval of a generic version of a solid oral opioid drug product that references an opioid drug product with abuse-deterrent properties described in its labeling. The guidance recommends studies, including comparative in vitro and pharmacokinetic (PK) studies, that a potential ANDA applicant should conduct and submit to FDA to demonstrate that a generic solid oral opioid drug product is no less abuse deterrent than its reference listed drug (RLD) with respect to all potential routes of abuse.

DATES: Submit either electronic or written comments on Agency guidances at any time.

ADDRESSES: You may submit comments as follows:

*Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

#### *Written/Paper Submissions*

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

*Instructions:* All submissions received must include the Docket No. FDA-2016-D-0785 for "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid

Drugs; Guidance for Industry; Availability.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

*Docket:* For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the

prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document. FOR FURTHER INFORMATION CONTACT: Gail Schmerfeld, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-9291, email: [gail.schmerfeld@fda.hhs.gov](mailto:gail.schmerfeld@fda.hhs.gov).

#### SUPPLEMENTARY INFORMATION:

##### I. Background

FDA is announcing the availability of a guidance for industry entitled “General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products.” Prescription opioid analgesics are an important component of modern pain management. However, abuse and misuse of these drug products have created a serious and widespread public health problem. Addressing this public health crisis is an FDA priority. One potentially important step toward the goal of creating safer opioid analgesics has been the development of opioid drug products that are formulated to deter abuse. “Abuse-deterrent properties,” as that term is used in the guidance to which this notice applies are those properties shown to meaningfully *deter* abuse; abuse-deterrent properties do not fully *prevent* abuse or addiction. FDA considers the development of these products a high public health priority. It is important that less costly

generic versions of opioids that reference listed drugs whose labeling describes abuse-deterrent properties are available to ensure access to safe and effective analgesics for patients who need them.

If the summary in section 9.2 of the approved labeling for the RLD indicates that FDA has concluded that the RLD has properties that are expected to (or have been shown through postmarketing studies to) deter abuse, the potential ANDA applicant should evaluate its proposed generic drug to show that it is no less abuse deterrent than the RLD with respect to *all* of the potential routes of abuse. This will ensure the generic drug is no less abuse-deterrent than the RLD with respect to all potential routes of abuse and minimize the risk of shifting abuse to other, potentially more dangerous routes. This guidance describes FDA's current thinking on the studies that should be conducted by a potential ANDA applicant and submitted to FDA in an ANDA to demonstrate that a generic solid oral opioid drug product is no less abuse deterrent than its RLD with respect to all potential routes of abuse. These studies are in addition to other studies that may be needed to support ANDA approval (e.g., as described in product-specific guidances).

The final guidance, like the draft guidance, focuses on the general principles for developing and evaluating the abuse deterrence of generic solid oral opioid drug products formulated to incorporate physical or chemical barriers, agonist/antagonist combinations, aversive agents, or a combination of two or more of these technologies. FDA will continue to assess the state of science and, as novel technologies develop, will address them by issuing additional guidance, as appropriate.

In the *Federal Register* of March 25, 2016, FDA announced the availability of the draft guidance for industry "General Principles for Evaluating the Abuse Deterrence of Generic Solid

Oral Opioid Drug Products” (81 FR 16186). FDA subsequently announced in the *Federal Register* of October 6, 2016, and held on October 31-November 1, 2016, a public meeting to discuss scientific and technical issues relating to formulation development and premarket evaluation of opioid drug products with abuse-deterrent properties (81 FR 69532). This final guidance reflects our consideration of comments made in the dockets for the draft guidance (Docket No. FDA-2016-D-0785) and for the public meeting (Docket No. FDA-2016-N-2896) and comments made during the public meeting, and provides the Agency’s current thinking with respect to the general principles for evaluating the abuse deterrence of generic solid oral opioid drug products.

Among other changes, the final guidance eliminates the recommendation to use a control to identify discriminatory study conditions for comparing the proposed generic opioid drug product (the test (T) product) and the RLD (reference (R) product). Instead, FDA recommends that a potential ANDA applicant conduct extraction studies to assess the particular vulnerabilities of T and R products to inform the comparison of their abuse deterrence. The final guidance also provides more detailed recommendations regarding the conduct of in vivo studies, specifically comparative PK studies of manipulated T and R products to evaluate the potential for abuse by the oral and nasal routes of administration.

Appendix 1 of the final guidance continues to describe some of the ways in which the T and R products can be physically manipulated and provides recommendations for conducting extraction studies to assess the particular vulnerabilities of the T and R products to inform the comparison of their abuse deterrence. FDA continues to recommend potential ANDA applicants follow a tier-based approach to extractability testing to efficiently compare a T product to its R

product and limit the number of tests required for evaluating the abuse deterrence of the T product, but has modified some of the initial recommendations regarding solvents.

Appendix 2 provides recommendations for evaluating abuse by ingestion. In the final guidance, FDA clarifies the circumstances under which a potential applicant should conduct a comparative oral PK study. Appendices 3, 4, and 5 provide modified recommendations for evaluating abuse by injection, insufflation, and smoking, respectively.

The guidance addresses the general principles for evaluating abuse deterrence in generic solid oral opioid drug products. FDA may provide additional testing recommendations in future product-specific guidances. For example, FDA may recommend in a product-specific guidance that a potential ANDA applicant evaluate human abuse potential (for example, evaluate a study subject's willingness to take drug again) if R product contains a known aversive agent. Further, FDA will continue to assess the state of the science and, as novel technologies develop, will address them by issuing revised or additional guidance, as appropriate.

Potential ANDA applicants may pose questions regarding evaluation of abuse deterrence for a generic solid oral opioid drug product through FDA's pre-ANDA program. The goals of the pre-ANDA program are to clarify regulatory expectations for prospective applicants early in the development process, assist applicants in developing more complete submissions, promote a more efficient and effective ANDA review process, and reduce the number of review cycles required to obtain ANDA approval, particularly for complex products. FDA considers abuse-deterrent opioids to be products that fall within the definition of *complex product* as that term has been defined in the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022, which can be found at <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>.

The pre-ANDA program provides for, among other things, submission of controlled correspondence and requests for formal meetings between FDA and applicants on complex generic drug development issues.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products." 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. This guidance is not subject to Executive Order 12866.

## II. Electronic Access

Persons with access to the internet may obtain the guidance at either <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <https://www.regulations.gov>.

Dated: November 16, 2017.

Anna K. Abram,

Deputy Commissioner for Policy, Planning, Legislation, and Analysis.  
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