



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2007-D-0369]

Product-Specific Guidance on Estradiol; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing the availability of a new draft guidance for industry entitled “Draft Guidance on Estradiol” and a revised draft guidance for industry entitled “Draft Guidance on Estradiol.” The new draft guidance and the revised draft guidance, when finalized, will provide product-specific recommendations on, among other things, the design of bioequivalence (BE) studies to support abbreviated new drug applications (ANDAs) for estradiol vaginal inserts and estradiol vaginal tablets.

DATES: Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance at any time 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-2007-D-0369 for "Draft Guidance on Estradiol." 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, 240-402-7500.

- 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.govinfo.gov/content/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, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft 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 draft guidance document.

FOR FURTHER INFORMATION CONTACT: Joseph Kotsybar, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 75, Rm. 3623A, Silver Spring, MD 20993-0002, 240-402-1062, PSG-Questions@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

In the *Federal Register* of June 11, 2010 (75 FR 33311), FDA announced the availability of a guidance for industry entitled “Bioequivalence Recommendations for Specific Products” that explained the process that would be used to make product-specific guidances available to the public on FDA’s website at <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>.

As described in that guidance, FDA adopted this process as a means to develop and disseminate product-specific guidances and provide a meaningful opportunity for the public to consider and comment on those guidances. This notice announces the availability of a new draft product-specific guidance on generic estradiol vaginal inserts and a revised draft product-specific guidance on generic estradiol vaginal tablets.

FDA initially approved new drug application (NDA) 208564 IMVEXXY (estradiol) in May 2018. We are now issuing a draft guidance for industry on, among other things, BE recommendations for generic estradiol vaginal inserts that use IMVEXXY as the reference listed drug (RLD) (“Draft Guidance on Estradiol” (vaginal inserts)). FDA initially approved NDA 020908 VAGIFEM (estradiol) in March 1999. We are also now issuing a revised draft guidance for industry on, among other things, BE recommendations for generic estradiol vaginal tablets that use VAGIFEM as the RLD (“Draft Guidance on Estradiol” (vaginal tablets)).

In December 2018 and May 2020, TherapeuticsMD, Inc. submitted citizen petitions requesting, among other things, that FDA not approve any ANDA referencing IMVEXXY (estradiol vaginal inserts) unless certain criteria are met and that FDA issue a product-specific guidance for generic estradiol vaginal inserts that recommends studies consistent with those requested in the petitions and includes certain BE recommendations for generic estradiol vaginal inserts that are consistent with the then-current version of “Draft Guidance on Estradiol” (vaginal tablets) (Docket No. FDA-2018-P-4714 and Docket No. FDA-2020-P-1334, available at

<https://www.regulations.gov>). FDA is separately responding to TherapeuticsMD, Inc.'s citizen petitions.

These draft guidances are being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidances, when finalized, will represent the current thinking of FDA on "Draft Guidance on Estradiol" (vaginal inserts; vaginal tablets). They do not establish any rights for any person and are not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

As we develop any final guidance on this topic, FDA will consider comments on costs or cost savings the guidance may generate, relevant for Executive Order 14192.

II. Paperwork Reduction Act of 1995

While these guidances contain no collection of information, they do refer to previously approved FDA collections of information. The previously approved collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The collections of information in 21 CFR part 312 for investigational new drugs have been approved under OMB control number 0910-0014. The collections of information in 21 CFR part 314 for applications for FDA approval to market a new drug and in 21 CFR part 320 for bioavailability and bioequivalence requirements have been approved under OMB control number 0910-0001.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>, or <https://www.regulations.gov>.

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