

*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 guidance to the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855. 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 See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.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:** Susan Storey, Center for Veterinary Medicine (HFV-131), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 240-402-0578, [susan.storey@fda.hhs.gov](mailto:susan.storey@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:**

**I. Background**

FDA is announcing the availability of draft GFI #267 entitled “Biomarkers and Surrogate Endpoints in Clinical Studies to Support Effectiveness of New Animal Drugs.” Section 305 of the Animal Drug and Animal Generic Drug User Fee Amendments of 2018 (Pub. L. 115-234), among other things, directed FDA to hold a public meeting for interested parties to discuss innovative animal drug investigation designs and to issue guidance addressing the incorporation of the use of such elements of investigations as complex adaptive and other novel investigation designs, data from foreign countries, real-world evidence (including ongoing surveillance activities, observational studies, and registry data), biomarkers, and surrogate endpoints into proposed clinical investigation protocols and applications for new animal drugs.

In the **Federal Register** of July 9, 2019 (84 FR 32749), FDA’s Center for Veterinary Medicine (CVM) published a notice of a public meeting entitled “Incorporating Alternative Approaches in Clinical Investigations for New Animal Drugs” giving interested persons until August 17, 2019, to comment on the topics discussed at the public meeting and the questions published in the meeting notice (84 FR

32749 at 32750 to 32751).<sup>1</sup> On August 13, 2019, we published a notice announcing the extension of the comment period to September 16, 2019 (84 FR 40071). CVM received numerous comments on the topics discussed at the public meeting and the questions published in the meeting notice and those comments were considered as the draft GFI #267 was developed.

This draft guidance describes how CVM intends to evaluate biomarkers, including surrogate endpoints, when they are incorporated into clinical investigations submitted to CVM to demonstrate substantial evidence of effectiveness for new animal drug applications or a reasonable expectation of effectiveness for applications for conditional approval of a new animal drug. It also provides information about how sponsors may obtain feedback from CVM on technical issues related to the use of biomarkers before the submission of an application.

This level 1 draft guidance is being issued consistent with FDA’s good guidance practices regulation (21 CFR 10.115). The draft guidance, if finalized, will represent the current thinking of FDA regarding the use of biomarkers, including surrogate endpoints, to support the effectiveness of new animal drugs. 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.

**II. Paperwork Reduction Act of 1995**

FDA tentatively concludes that this draft guidance contains no collection of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required.

However, this draft guidance refers to previously approved FDA collections of information found in FDA regulations for new animal drug applications submitted under sections 512(b) (21 U.S.C. 360b(b)) and 571 of the FD&C Act. These collections of information are subject to review by the OMB under the PRA. The collections of information in 21 part 514 have been approved under OMB control number 0910-0032.

**III. Electronic Access**

Persons with access to the internet may obtain the draft guidance at either <https://www.fda.gov/animal-veterinary/>

<sup>1</sup> <https://www.fda.gov/animal-veterinary/workshops-conferences-meetings/public-meeting-incorporating-alternative-approaches-clinical-investigations-new-animal-drugs>.

[guidance-regulations/guidance-industry](https://www.regulations.gov) or <https://www.regulations.gov>.

Dated: July 9, 2020.

**Lowell J. Schiller,**

*Principal Associate Commissioner for Policy.*

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**BILLING CODE 4164-01-P**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. FDA-2020-D-1400]

**Use of Real-World Data and Real-World Evidence To Support Effectiveness of New Animal Drugs; Draft 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 draft guidance for industry (GFI) #266 entitled “Use of Real-World Data and Real-World Evidence to Support Effectiveness of New Animal Drugs.” The draft guidance, if finalized, will describe FDA’s current thinking with respect to assisting sponsors in incorporating real-world data and real-world evidence (including ongoing surveillance activities, observational studies, and registry data) into proposed clinical investigation protocols and applications for new animal drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

**DATES:** Submit either electronic or written comments on the draft guidance by October 13, 2020 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-2020-D-1400 for “Use of Real-World Data and Real-World Evidence to Support Effectiveness of New Animal Drugs.” 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>.

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**FOR FURTHER INFORMATION CONTACT:** Susan Storey, Center for Veterinary Medicine (HFV-131), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 240-402-0578, [susan.storey@fda.hhs.gov](mailto:susan.storey@fda.hhs.gov).

#### SUPPLEMENTARY INFORMATION:

##### I. Background

FDA is announcing the availability of draft GFI #266 entitled “Use of Real-World Data and Real-World Evidence to Support Effectiveness of New Animal Drugs.” Section 305 of the Animal Drug and Animal Generic Drug User Fee Amendments of 2018 (Pub. L. 115-234), among other things, directed FDA to hold a public meeting for interested parties to discuss innovative animal drug investigation designs and to issue guidance addressing the incorporation of the use of such elements of investigations as complex adaptive and other novel investigation designs, data from foreign countries, real-world evidence (including ongoing surveillance activities, observational studies, and registry data), biomarkers, and surrogate endpoints into proposed clinical investigation protocols and applications for new animal drugs.

In the **Federal Register** of July 9, 2019 (84 FR 32749), FDA’s Center for

Veterinary Medicine (CVM) published a notice of a public meeting entitled “Incorporating Alternative Approaches in Clinical Investigations for New Animal Drugs” giving interested persons until August 17, 2019, to comment on the topics discussed at the public meeting and the questions published in the meeting notice (84 FR 32749 at 32750 to 32751). On August 13, 2019, we published a notice announcing the extension of the comment period to September 16, 2019 (84 FR 40071). CVM received numerous comments on the topics discussed at the public meeting and the questions published in the meeting notice and those comments were considered as the draft GFI #266 was developed.

This draft guidance describes how CVM intends to evaluate real-world data and real-world evidence in submissions to CVM to demonstrate substantial evidence of effectiveness for new animal drug applications or a reasonable expectation of effectiveness for applications for conditional approval of a new animal drug. It also provides information about how sponsors may obtain feedback from CVM on technical issues related to the use of real-world data and real-world evidence before the submission of an application.

This level 1 draft guidance is being issued consistent with FDA’s good guidance practices regulation (21 CFR 10.115). The draft guidance, if finalized, will represent the current thinking of FDA regarding the use of real-world data and real-world evidence (including ongoing surveillance activities, observational studies, and registry data) in submissions to CVM to support the effectiveness of new animal drugs. 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.

##### II. Paperwork Reduction Act of 1995

FDA tentatively concludes that this draft guidance contains no collection of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required.

However, this draft guidance refers to previously approved FDA collections of information found in FDA regulations for new animal drug applications submitted under section 512(b) (21 U.S.C. 360b(b)) and 571 (21 U.S.C. 360ccc-1) of the FD&C Act. These collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR

part 514 have been approved under OMB control number 0910-0032.

### III. Electronic Access

Persons with access to the internet may obtain the draft guidance at either <https://www.fda.gov/animal-veterinary/guidance-regulations/guidance-industry> or <https://www.regulations.gov>.

Dated: July 9, 2020.

**Lowell J. Schiller,**

*Principal Associate Commissioner for Policy.*

[FR Doc. 2020-15243 Filed 7-14-20; 8:45 am]

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-1984-N-0259 (formerly 84N-0167)]

#### Vasodilan Injection and Tablets Containing Isoxsuprine Hydrochloride; Final Decision on Proposal To Withdraw Approval of New Drug Application; Availability of Final Decision

**AGENCY:** Food and Drug Administration; Health and Human Services (HHS).

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA or the Agency) is announcing that the Initial Decision of the Administrative Law Judge (ALJ), that Vasodilan containing Isoxsuprine Hydrochloride had not been shown to be supported by substantial evidence consisting of adequate and well-controlled studies to be effective for treating symptoms relating to senile dementia of the Alzheimer type (SDAT) and multiple infarct dementia and peripheral vascular disease, is the final decision of the Commissioner of Food and Drugs (the Commissioner).

**DATES:** This notice is applicable July 15, 2020.

**ADDRESSES:** For access to the docket, 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 between 9 a.m. and 4 p.m., Monday through Friday. Publicly available submissions may be seen in the docket.

**FOR FURTHER INFORMATION CONTACT:** Rachael Vieder Linowes, Office of Scientific Integrity, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, Rm. 4206, Silver Spring, MD 20993, 240-402-5931.

**SUPPLEMENTARY INFORMATION:** Several parties to the hearing, including the new drug application (NDA) holder and identical, related, or similar (IRS) product manufacturers, filed exceptions to the ALJ's Initial Decision. FDA recently requested that the current owner of the NDA and successors-in-interest to IRS product manufacturers who submitted timely exceptions to the ALJ's Initial Decision affirm, within a specific timeframe, their interest in pursuing their appeals of the ALJ's Initial Decision. FDA did not receive any responses within the specified timeframe. Accordingly, FDA now deems those exceptions as withdrawn. Consequently, the proceeding is in the same procedural position as if no exceptions to the ALJ's Initial Decision had been filed. Therefore, the ALJ's Initial Decision has become the final decision of the Commissioner by operation of law.

### I. Background

In 1962, the Federal Food, Drug, and Cosmetic Act (FD&C Act) was amended by the Drug Amendments Act of 1962, and these amendments provided that new drugs could no longer be approved unless both safety and efficacy had been established for them. As amended, the FD&C Act also required FDA to evaluate drugs approved as safe between 1938 and 1962 to determine whether such drugs were effective and to withdraw approval for any NDA where there was not substantial evidence of the drug's effectiveness. The person contesting the withdrawal of the approval had the burden of coming forward with evidence of effectiveness for the drug. FDA's review of these pre-1962 drugs is known as the Drug Efficacy Study Implementation program.

In a notice published in the **Federal Register** of July 11, 1972 (37 FR 13565, available at <https://www.govinfo.gov/content/pkg/FR-1972-07-11/pdf/FR-1972-07-11.pdf>), after receiving reports from the National Academy of Sciences/National Research Council, Drug Efficacy Study Group, FDA stated that Vasodilan Injection and Tablets containing Isoxsuprine Hydrochloride lacked substantial evidence of effectiveness for several indications. In a notice published in the **Federal Register** of May 25, 1979 (44 FR 30443, available at <https://www.govinfo.gov/content/pkg/FR-1979-05-25/pdf/FR-1979-05-25.pdf>), the Director of the Bureau of Drugs (now the Center for Drug Evaluation and Research), after reviewing all the data previously submitted, concluded that Vasodilan lacks substantial evidence of effectiveness for its labeled indications,

and proposed to withdraw approval of the NDA and issued a notice of opportunity for hearing on a proposal to withdraw approval of Vasodilan.

Mead Johnson, the NDA holder of Vasodilan (NDA 11-832) submitted data intended to support the effectiveness of Vasodilan for other indications, including: (1) Relief of symptoms associated with SDAT and/or multiple infarct dementia; (2) relief of symptoms associated with peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans, and Raynaud's disease; and (3) relief of symptoms of uterine motility, including premature labor, dysmenorrhea, and threatened abortion.

Mead Johnson and multiple IRS product manufacturers responded to the notice of opportunity for a hearing and submitted requests for a hearing. By notice published in the **Federal Register** on September 28, 1984 (49 FR 38363, available at <https://www.govinfo.gov/content/pkg/FR-1984-09-28/pdf/FR-1984-09-28.pdf>), the Commissioner granted a hearing; however, the Commissioner only granted a hearing concerning the use of Vasodilan in treating symptoms related to: (1) SDAT or multiple infarct dementia and (2) peripheral vascular disease. Although Mead Johnson requested a hearing on the issue of Vasodilan's effectiveness in relieving symptoms of uterine motility, including premature labor, dysmenorrhea, and threatened abortion, Mead Johnson later abandoned this indication and consented to withdrawal of Vasodilan's approval for it (see *id.*). Following the submission of written testimony and documentary evidence, an ALJ, Daniel J. Davidson, conducted a hearing and issued his Initial Decision on August 20, 1986. The ALJ found that the effectiveness of Vasodilan had not been shown to be supported by substantial evidence and, as a result, ordered that the approval of the NDA be withdrawn. Mead Johnson and certain IRS product manufacturers timely appealed the ALJ's Initial Decision by filing exceptions with the Commissioner under 21 CFR 12.125.

Separately, by notice published in the **Federal Register** of February 11, 2009 (74 FR 6896), FDA withdrew approval of Vasodilan. The current NDA holder and successor to Mead Johnson, Apothecon, c/o Bristol-Myers Squibb Co. (BMS), had requested that FDA withdraw approval of the application because the drug product was no longer marketed; additionally, BMS waived its opportunity for a hearing on the withdrawal.

On November 9, 2017, FDA sent letters to BMS and the successors-in-