



**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**[Docket No. FDA-2019-N-5464]**

**Novel Excipient Review Program Proposal; Request for Information and Comments**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice; request for information and comments.

**SUMMARY:** The Food and Drug Administration (FDA, the Agency, or we) is announcing the establishment of a docket to obtain information and comments that will assist the Agency in determining whether it should establish a pilot program for the toxicological and quality evaluation of novel excipients intended for use in human drugs. The Agency hopes to obtain information and comments on several aspects of such a program before deciding whether to develop it.

**DATES:** Submit written or electronic comments and information on the notice by **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

**ADDRESSES:** You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

### *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-2019-N-5464 for "Novel Excipient Review Program Proposal; Request for Information and Comments." Received comments, those filed in a timely manner (see ADDRESSES), 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 docket, 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.

**FOR FURTHER INFORMATION CONTACT:** Karen Davis Bruno, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6428, Silver Spring, MD 20993-0002, 301-796-1199, [karen.davisbruno@fda.hhs.gov](mailto:karen.davisbruno@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:**

I. Background

We use the term "excipient" in this notice to mean any ingredient intentionally added to a drug product (including biological drug products) that is not intended to exert therapeutic effects at the intended dosage, although it may improve product delivery (see FDA guidance for industry "Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients" (Excipients guidance), May 2005, p. 1 (available at <https://www.fda.gov/media/72260/download>)). The term "inactive ingredient" is often used to mean the same thing. Examples of excipients include fillers, extenders, diluents, wetting agents, solvents, emulsifiers, preservatives, flavors, absorption enhancers, sustained-release matrices, and coloring agents (see Excipients guidance, pp. 1-2). For purposes of this notice, FDA would expect a novel excipient to be an excipient that has not been previously used in FDA-approved drug products and that does not have established use in food.

FDA reviews excipients used in a drug product as part of an investigational new drug application (IND) or a marketing application to determine whether they are safe for use in human

pharmaceuticals. Historically, FDA has not reviewed the safety of novel excipients outside the context of an IND, a new drug application (NDA), or a biologics license application (BLA) describing a finished product to which the excipient has been added.<sup>1</sup>

Stakeholders have encouraged FDA to establish a program for the submission and review of toxicological and quality data supporting the use of novel excipients in drug products outside the context of an IND, an NDA, or a BLA. They state that certain novel excipients may provide public health benefits, such as improved drug delivery or utility in abuse-deterrent opioid formulations, for example. Proponents of an FDA novel excipient review program believe FDA's recognition of a novel excipient would reassure drug developers that the novel excipient can be used in a drug development program while minimizing the risk that safety concerns would be raised by FDA during application review. They have also cited a perceived risk aversion on the part of drug developers, such that novel excipients may be avoided in drug development programs, even when the excipients have potential public health benefits.

With this information in mind, FDA's Center for Drug Evaluation and Research is considering developing a pilot program for the toxicological and quality evaluation of novel excipients. The Agency seeks information and comment on several aspects of such a program before deciding whether to develop it.

## II. Possible Approach to Reviewing Novel Excipients

FDA is considering establishing a pilot program that would review a limited number of submissions per year. Any program developed by the Agency would be voluntary. FDA

---

<sup>1</sup> A proposed drug product that contains an excipient that would require clinical investigations to establish safety of the excipient for use in a particular drug product would not be permitted in an abbreviated new drug application (ANDA) but may be submitted in a 505(b)(2) application.

recognition of a novel excipient would not be necessary for the novel excipient to be included in a finished drug product described in an IND, an NDA, or a BLA.

Generally, FDA anticipates that a submission to a potential novel excipient review program would include toxicological studies supporting the safety of the novel excipient at anticipated levels and duration of exposure, by anticipated routes of administration.

Additionally, FDA anticipates that submitters would provide identification and control information, including compositional and purity specifications for the novel excipient (see Excipients guidance).

FDA recognition of a novel excipient would mean that, based on a review of safety, manufacturing, and compositional information, FDA has determined that the proposed context of use (e.g., acute or chronic exposure by specified route(s) of administration up to specified amounts) is expected to be safe. This determination would obviate the need for FDA review of the excipient in the context of an IND if its use in the investigational product is consistent with the recognized context of use. In the case of an NDA or a BLA seeking marketing approval or licensure of a finished drug or biological product containing a recognized excipient, FDA would review all information in the application relating to safety of the finished product. FDA expects that excipients reviewed under this program, after they are used in approved formulations, would be listed in the Inactive Ingredient Database.

### III. Requested Information and Comments

Interested persons are invited to provide detailed comment on all aspects of this issue. Please read the information above regarding the submission of comments and confidential information. FDA is particularly interested in responses to the following questions:

1. What drug development challenges do drug sponsors encounter that could be addressed by using novel excipients?
2. Can stakeholders identify examples (specific or general) of novel excipients that have potential public health benefits?
3. FDA anticipates that a novel excipient recognition program would be limited to excipients that do not have a well-established history of safe use in food and that have potential public health benefits. We would be interested in stakeholder comment on these criteria.
4. Would FDA recognition of a novel excipient be sufficient to overcome any reluctance on the part of drug developers to use the novel excipient in a drug development program?  
Do drug development sponsors also look for a history of safe use in marketed drug products?
5. FDA envisions that an individual excipient manufacturer participating in a novel excipient recognition program would submit a complete package of safety data and certain chemistry, manufacturing, and controls information to support FDA's recognition of a novel excipient. This data and information would be based upon nonclinical studies of sufficient quality and quantity to allow for a safety evaluation, consistent with the Excipients guidance. We would be interested in stakeholder comment on this approach.
6. Are there adequate incentives for excipient manufacturers to engage in this process, particularly in situations in which multiple manufacturers may be undertaking to develop closely related novel excipients? If not, what incentives would encourage excipient manufacturers to engage in this process?

7. What information, if any, should FDA affirmatively disclose about a novel excipient evaluated under an eventual program in order to ensure the success of the program? For example, should FDA's evaluation be posted and explained publicly? Please note that FDA would handle disclosure of information submitted under the program in accordance with applicable law.

Dated: December 2, 2019.

**Lowell J. Schiller,**

*Principal Associate Commissioner for Policy.*

[FR Doc. 2019-26266 Filed: 12/4/2019 8:45 am; Publication Date: 12/5/2019]