4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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

Center for Drug Evaluation and Research Office of New Drugs Novel Excipient Review Pilot Program

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) is announcing a Novel Excipient Review Pilot Program (Pilot Program). The Pilot Program is voluntary and intended to allow excipient manufacturers to obtain FDA review of certain novel excipients prior to their use in drug formulations. The Pilot Program seeks to foster development of excipients that may be useful in scenarios in which excipient manufacturers and drug developers have cited difficulty in using existing excipients.

DATES: FDA is seeking initial proposals for the voluntary Novel Excipient Review Pilot Program through **[INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

FOR FURTHER INFORMATION CONTACT: Felecia Wilson, Center for Drug Evaluation and Research, Food and Drug Administration, Novel-Excipient-Program@fda.hhs.gov, 301-796-9590.

SUPPLEMENTARY INFORMATION:

I. Background

Excipient manufacturers and drug developers have cited product development challenges related to the use of certain excipients (also known as inactive ingredients), including issues related to formulation and stability. Novel excipients might be able to address some of these issues and provide additional public health benefits, such as enhanced drug bioavailability, more

comfortable drug administration, new abuse-deterrent opioid formulations, new routes of drug delivery, and facilitation of new technologies. However, drug developers report that they have been hesitant to use novel excipients in drug development programs due to the uncertainty surrounding their acceptability.

To address these issues, FDA issued a request for information in the *Federal Register* on December 5, 2019 (84 FR 66669), seeking comment on a potential pilot program for FDA review of novel excipients. FDA received several comments to the public docket on these issues. After considering these comments, CDER has decided to establish this Pilot Program.

A. Scope

For purposes of the Pilot Program, an *excipient* is any ingredient intentionally added to a drug product (including a biological drug product) that is not intended to exert therapeutic effects at the intended dosage, although it may improve product delivery (see FDA guidance for industry entitled "Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients" (Ref.1)). Examples of excipients may include fillers, extenders, diluents, surfactants, solvents, emulsifiers, preservatives, flavors, absorption enhancers, modified release matrices, and coloring agents. Also, for purposes of this Pilot Program, a *novel excipient* is any excipient that is not fully supported by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration (Ref. 1). This parallels the definition of "new excipients" defined in Ref. 1.

CDER proposes a more limited scope for this Pilot Program. The Pilot Program will initially be available for novel excipients that (1) have not been previously used in FDA-approved drug products, and (2) do not have an established use in food. CDER recognizes that there may be novel excipients not meeting this scope that may also address product development challenges or provide public health benefits. However, because of the limited scope of the initial phase of the Pilot Program (described further below), CDER will not be able to consider

submissions for all kinds of novel excipients. CDER may expand the scope of the Pilot Program in the future depending on its success and as resources allow.

The Pilot Program is voluntary. Existing processes for developing excipients for use in drug and biological products continue to be available.

B. Participation

The Pilot Program will consist of two stages. The first stage is an initial proposal stage for excipient manufacturers to provide a high-level overview of their novel excipient. CDER intends to accept approximately four initial proposals (two for the first year of the Pilot Program, and two for the second year) but will consider accepting more proposals as resources allow. Excipient manufacturers whose initial proposals are accepted would then enter the second stage, during which they would provide a full data package consisting of toxicology and quality data. Both stages are described in further detail below.

As mentioned above, CDER intends to consider for the Pilot Program novel excipients that (1) have not been previously used in FDA-approved drug products, and (2) do not have an established use in food.

C. Procedures

1. Initial Proposal Stage

At the initial proposal stage, excipient manufacturers will submit brief summaries describing the novel excipient, its proposed use, and the public health or drug development need addressed by the excipient. The initial proposal is anticipated to include a summary of the supportive data generated or collected so far and some indication of the timing of any subsequent data needed for submission of the Full Package. FDA has posted an initial proposal model content outline on the Pilot Program web page (https://www.fda.gov/drugs/development-approval-process-drugs/novel-excipient-review-pilot-program).

Interested excipient manufacturers should submit initial proposals to FDA via email at Novel-Excipient-Program@fda.hhs.gov. FDA will accept proposals for the pilot through

[INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. FDA will notify all submitters whether their proposal is accepted into the Pilot Program.

FDA will review the initial proposals and select approximately four proposals (two for the first year and two for the second year) to proceed to stage two of the program. FDA will consider the following factors, among other considerations, in determining which proposals to select:

- Potential public health benefit of the novel excipient (for example, excipients that may facilitate opioid abuse-deterrent formulations or excipients that may promote development of new therapies for serious and life-threatening diseases).
- Likelihood of the novel excipient manufacturer's ability to submit a complete package within the timeframe established in this Notice.
- Overall potential of the novel excipient to meaningfully improve pharmacokinetic characteristics that may lead to novel drug development.

2. Procedures for Full Packages

For novel excipients selected into the program, the developer should submit a full package consisting of toxicology and quality data as described below. See CDER Guidance for industry entitled "Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients" (Ref. 1).

a. Toxicology data package. The toxicology data package should include adequate, supportive safety information for the novel excipient to verify that the proposed excipient is safe in the amounts and type of product(s) in which it may be administered as well as the proposed use (e.g., level, route, duration, patient population). Depending on the proposed use, the toxicology data package may include the information described below. Additional safety data may be requested if the proposed use is not fully supported by the available data. Reference is made to the relevant guidance for the proposed toxicology data package below.

- Safety pharmacology: Novel excipients should be evaluated for pharmacological activity using a battery of standard tests (see FDA guidance for industry entitled "S7A Safety Pharmacology Studies for Human Pharmaceuticals" (Ref. 2)).
- Pharmacokinetic testing (absorption, distribution, metabolism, and excretion): To determine the extent of exposure. A pharmacokinetic profile for an excipient that is extensively absorbed, undergoes extensive biotransformation, or both will be useful.
- General toxicology: Chronic, 6-month repeat dose toxicology studies in a relevant species by appropriate route with complete clinical pathology, histopathology, and toxicokinetic analysis are recommended. Because excipients generally have low toxicity, the limit dose is recommended as the highest dose for testing (see FDA guidance for industry entitled "M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals" (Ref. 3)).
- Genetic toxicology (see FDA guidance for industry entitled "S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals" (Ref. 4)).
- Reproductive toxicology: Fertility, embryo-fetal, and pre- and post-natal development (see International Council for Harmonization harmonized guidance for industry entitled "Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals S5(R3)" (Ref. 5)).
- Carcinogenicity: One of the following approaches may be used to evaluate carcinogenic potential (see FDA guidance for industry entitled "The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals" (Ref. 6)):
    - Two-year carcinogenicity bioassays in two appropriate species by the relevant route;
    - A 2-year carcinogenicity study in rat plus a transgenic mouse model; or

    - Submission of documentation providing scientific justification that carcinogenicity data are not necessary based on the weight of evidence approach in an assessment to address the carcinogenic potential.
- Special studies (e.g., local tolerance, Juvenile Animal Studies).

b. Quality data package. The novel excipient chemistry, manufacturing, and controls data submitted to CDER should be similar to that provided in an investigational new drug application (IND).

For evaluation of all novel excipients with a proposed use in formulations for small molecule and biological drug products reviewed by CDER/Office of New Drugs (OND), submitters should provide:

- Excipient specifications.
- A description of the source, synthetic pathway/fermentation or extraction for non-synthetic excipients, raw materials, in-process controls, manufacturing process description, characterization and analytical methods, or a letter of authorization (right of reference) for the excipient Type IV drug master file (DMF) or other master file if a master file has been submitted for the excipient.
- If the excipient contains a novel moiety with immunogenic potential, an immunogenicity risk assessment that may include in vitro data. Additional information on immunogenicity risk assessment may be found in FDA guidance for industry entitled "S8 Immunotoxicity Studies for Human Pharmaceuticals" for types of supporting in vitro studies (Ref. 7).
- If the excipient is sourced from cells, clearance of host cell protein (absence in final excipient) and evidence of absence of adventitious agents such as viruses.

In addition, for evaluation of novel excipients with a proposed use in formulations for biological drug products reviewed by CDER/OND, submitters should provide:

- Stability studies of the excipient under storage and potential in-use conditions (e.g., over infusion time). Novel excipients should be evaluated for their potential to prevent denaturation and degradation of proteins during storage.
- For some excipients, studies should address their potential protein-excipient interaction and impact on drug product immunogenicity as well as their potential for masking process related impurities.

Full packages should be submitted through a Type V DMF or other master file no later than 3 months after notification that FDA has selected the proposal. For more information on submitting Type V DMFs, see the FDA draft guidance for industry entitled "Drug Master Files" (Ref. 8).

FDA will evaluate the full package and determine whether the excipient is appropriate for the proposed use for use in clinical trials. FDA will issue a letter to the novel excipient submitter announcing its decision.

For each novel excipient evaluated under the second stage of the program, FDA will publish on the Pilot Program web page the initial proposal and the determination letter. Information that cannot be publicly disclosed will be redacted. This web page will also include a content outline identifying information that should be included in an Initial Proposal and other relevant information regarding the pilot.

3. Effect of Determination

A determination that the excipient is appropriate for use in clinical trials means that FDA has determined it is appropriate to use the novel excipient in an IND within the defined use without additional justification. However, the drug sponsor would still need to demonstrate that the excipient is safe in the proposed formulation. The information submitted under the full package would remain in the Type V DMF or other master file, and the master file holder may grant authorization to reference the information in the master file at the holder's discretion. Moreover, we do not anticipate that a novel excipient may be used in an abbreviated new drug

application because data and information currently required to support use of a novel excipient may not be submitted in an abbreviated new drug application. After it has been used in approved drug products, the novel excipient would be added to the Inactive Ingredient Database in accordance with Agency practice.

If FDA determines that the excipient is not appropriate for the proposed use, an IND sponsor would be expected to provide additional information to demonstrate that the use of the novel excipient is appropriate within the context of the IND.

II. Paperwork Reduction Act of 1995

The information collection activities associated with the Pilot Program refer to previously approved FDA collections 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 for this Pilot Program. The previously approved collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR part 314 pertaining to the submission of abbreviated new drug applications, new drug applications, and DMFs have been approved under OMB control number 0910-0001. The collections of information in 21 CFR part 312 pertaining to the submission of IND content and format; chemistry, control, and manufacturing data; pharmacology and toxicology data; and pharmacokinetics and biological data have been approved under OMB control number 0910-0014. The collections of information in 21 CFR part 58 pertaining to good laboratory practice regulations for nonclinical laboratory studies have been approved under OMB control number 0910-0119. The collections of information in 21 CFR part 601 pertaining to biologics license applications have been approved under OMB control number 0910-0338.

III. References

The following references are on display at the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500, and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday

through Friday; they are also available electronically at https://www.regulations.gov. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. FDA, Guidance for Industry, "Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients," May 2005 (available at https://www.fda.gov/media/72260/download). For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

2. FDA Guidance for Industry, "S7A Safety Pharmacology Studies for Human Pharmaceuticals," July 2001 (available at https://www.fda.gov/media/72033/download).

3. FDA, Guidance for Industry, "M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals," January 2010 (available at https://www.fda.gov/media/71542/download).

4. FDA, Guidance for Industry, "S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals," July 1997 (available at https://www.fda.gov/media/71971/download).

5. International Council for Harmonization (ICH), Guidance for Industry, "Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals S5(R3)," February 2020 (available at https://database.ich.org/sites/default/files/S5-R3_Step4_Guideline_2020_0218_1.pdf).

6. FDA, Guidance for Industry, "The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals," March 1996 (available at https://www.fda.gov/media/71921/download).

7. FDA, Guidance for Industry, "S8 Immunotoxicity Studies for Human Pharmaceuticals," April 2006 (available at https://www.fda.gov/media/72047/download).

8. FDA, Draft Guidance for Industry "Drug Master Files," October 2019 (available at https://www.fda.gov/media/131861/download).

Dated: September 1, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

[FR Doc. 2021-19335 Filed: 9/7/2021 8:45 am; Publication Date: 9/8/2021]