4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-N-4414]

Established Conditions; Pilot Program

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency), Center for Drug Evaluation and Research (CDER) is announcing the opportunity for a limited number of applicants to participate in an Established Conditions Pilot Program, to propose explicit established conditions (ECs) as part of an original new drug application (NDA), abbreviated new drug application (ANDA), biologics license application (BLA), or as a prior approval supplement (PAS) to any of these. The concept of ECs was first described in the FDA draft guidance for industry entitled "Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products", issued May 2015 and has been further discussed in the International Council for Harmonisation (ICH) draft guidance for industry entitled "Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management; International Council for Harmonisation", issued May 30, 2018. FDA is implementing this pilot program to gain experience receiving, assessing, and engaging with applicants regarding proposed ECs (i.e., explicit ECs).

DATES: FDA will accept nine requests submitted before May 30, 2019 from applicants intending to submit NDAs, ANDAs, or BLAs, either original applications or prior approval supplements, with proposed ECs.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Background

The concept of ECs was first described in the FDA draft guidance for industry entitled "Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products" (hereafter, "FDA guidance") issued May 2015 (80 FR 31050) and has been further discussed in the ICH draft guidance for industry entitled "Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management; International Council for Harmonisation", (hereafter "ICH Q12 guidance") issued May 30, 2018 (83 FR 25018).

The regulations at §§ 314.50(d)(1), 314.54(a)(1), and 314.94(a)(9) (21 CFR 314.50(d)(1), 314.54(a)(1), and 314.94(a)(9)) require that any NDA or ANDA submitted to the Agency contain a chemistry, manufacturing, and controls (CMC) section that describes information such as the composition of the drug product, manufacture of the drug substance, and manufacture of the drug product. Similarly, under § 601.2 (21 CFR 601.2), applicants submitting BLAs must also provide relevant CMC information, such as a full description of manufacturing methods and data establishing stability of the product through the dating period.

All changes after approval of an application must be managed and executed in conformance with current good manufacturing practice (CGMP), although §§ 314.70(a) and 601.12(a) only require a subset of changes to be reported to the FDA. Sections 314.70(a)(1)(i) and 314.97 require that, other than the exceptions or alternatives provided in § 314.70(a)(1)(ii),

an applicant notify FDA about each change in each condition established in an approved NDA or ANDA beyond the variations already provided for in the approved application. Per § 601.12(a)(1), an applicant must inform FDA about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved BLA.

After approval of an application, applicants desiring to make changes to this CMC information must evaluate the changes in the context of the regulations to determine if there is a need to report the change and associated supporting data and justifications to FDA. Although the reporting mechanism for many CMC changes has been made clear through publication of various guidance documents, FDA issued its draft guidance on ECs due to concern that there is confusion regarding which elements of an application are considered to be ECs. This confusion could have a negative impact on change management activities and could discourage continual improvement in product manufacturing processes, lead to unnecessary submission of postapproval supplements to FDA for changes that could be managed solely by a manufacturer's Pharmaceutical Quality System, or, upon inspection, lead to Form FDA 483 observations for changes that should have been reported to FDA. Moreover, a better understanding of which elements of the CMC information constitute ECs to FDA, and where in an application these elements are generally expected to be described, could allow for a more effective postapproval submission strategy (e.g., effective use of risk management principles in ICH Q9 "Quality Risk Management," and knowledge management as defined in ICH Q10 "Pharmaceutical Quality System") by the regulated industry.

In the FDA draft guidance, ECs are defined as the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy,

as defined in an application, that assure process performance and quality of an approved product. Changes to the ECs must be reported to FDA (§§ 314.70 and 601.12). This definition is consistent with the ICH Q12 guidance, which states that "ECs are legally binding information (or approved matters) considered necessary to assure product quality. Consequently, any change to ECs necessitates a submission to the regulatory authority."

Although each application submitted to the Agency contains ECs, as described in §§ 314.70(a) and 601.12(a), FDA has not specifically indicated the applicable ECs for each application at the time of approval. In addition, the draft ICH Q12 guidance describes how an applicant can specifically identify and propose so-called "explicit" ECs in which the EC itself or the reporting category for the EC, if changed, differs from existing requirements as described in regulations and guidance. Such explicit ECs should be supported by an appropriate justification that takes into consideration the applicant's development approach and risk to product quality. FDA recognizes that this process will be new for both applicants and Agency staff. Therefore, FDA is proposing this pilot program.

II. Objectives

The objectives of this pilot program are to gain practical experience in:

- assessing proposed ECs (i.e., explicit ECs);
- engaging with applicants during the review cycle to refine proposed ECs;
- ensuring assessment decisions are made without negatively impacting the ability to meet user fee timeframes; and
- identifying agreed-upon ECs at the time of approval.

FDA further encourages applicants who are accepted into this pilot program to pursue pre-submission meetings (pre-NDA, pre-BLA, or pre-ANDA, where appropriate) through

existing mechanisms. See, for example, FDA draft guidances entitled "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products and Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products" (once final, these guidance documents will represent FDA's current thinking on these topics) to improve the likelihood that a list of agreed-upon ECs can be reached prior to application approval. Although FDA's Center for Biologics Evaluation and Research (CBER) is not participating in this pilot, CBER intends to leverage CDER's experience from the pilot as CBER assesses explicit ECs in future submissions.

III. Requests to Participate

Parties who have an interest in participating in this Established Conditions Pilot Program and who plan to propose explicit ECs in an upcoming marketing application should submit a written request to the CDER-OPQ-Inquiries@fda.hhs.gov mailbox. The request should specify the request to participate in the Established Conditions Pilot Program.

The request should also include the following items:

1. The contact person's name, company name, and company contact information.
2. The proposed application type (NDA, ANDA, BLA; original or supplement).
3. The established name of the proposed product and a brief description (e.g., dosage form, indication).
4. Plans for any pre-NDA, pre-BLA, or pre-ANDA meetings to take place prior to application submission. Requests for such meetings should follow previously established procedures as outlined in relevant guidance documents.

5. Expected timing for submission of the application. The submission should be planned for receipt by FDA no later than July 1, 2019.
6. Acknowledgement that participation in the pilot program may be discontinued if the manufacturing facilities named in the application are not in a state of compliance with CGMP at the time of the application submission.

We intend to accept nine requests that meet the criteria above and represent a variety of application types, as Agency resources allow. FDA expects to notify companies of its decision regarding acceptance into the pilot program in writing within 60 days of receipt of the request. Although incomplete and/or unclear requests will generally be denied, FDA may contact the applicant to request additional information.

FDA intends to accept requests to participate starting on the date of publication of this notice.

IV. Paperwork Reduction Act of 1995

This notice refers to previously approved collections of information found in FDA regulations. These 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. 3501-3520).

The collections of information in 21 CFR part 314 for submitting NDAs and ANDAs have been approved under OMB control number 0910-0001, and the collections of information in 21 CFR part 601 for submitting BLAs has been approved under OMB control number 0910-0338.

FDA also has OMB approval under control number 0910-0429 for submissions under the guidance for industry entitled "Formal Meetings Between the FDA and Sponsors or Applicants,"

and under the guidance for industry "Controlled Correspondence Related to Generic Drug Development" (OMB control number 0910-0797).

V. References

The following references are on display in the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; these are also available electronically at https://www.regulations.gov. FDA 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 draft guidance for industry entitled "Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products" (May 2015), available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm448638.pdf.
2. FDA draft guidance for industry entitled "ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management" (May 2018), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM609205.pdf.
3. FDA draft guidance for industry entitled "Formal Meetings Between the FDA and Sponsors or Applicants for PDUFA Products" (December 2017), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf.
4. FDA draft guidance for industry entitled "Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products" (June 2018), available at

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM609662.pdf.

5. FDA draft guidance for industry entitled "Controlled Correspondence Related to Generic Drug Development" (November 2017), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM583436.pdf.

Dated: February 11, 2019.

Lowell J. Schiller,

Acting Associate Commissioner for Policy.

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