POLICY

OFFICE OF PHARMACEUTICAL QUALITY

Environmental Assessments and Claims of Categorical Exclusion

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PURPOSE

This MAPP summarizes the policy for the review of environmental assessments (EAs) and claims of categorical exclusion in new drug applications (NDAs), biologics license applications (BLAs), abbreviated new drug applications (ANDAs), or supplements to these applications (sNDAs, sBLAs, and sANDAs), and investigational new drug applications (INDs). This MAPP also outlines the responsibilities of the Regulatory Business Project Manager, Environmental Reviewer, and Quality Reviewer.

BACKGROUND

The National Environmental Policy Act of 1969 (NEPA) requires all federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of its actions, including approval of NDAs, ANDAs, BLAs, supplements to such applications, and actions on INDs, as part of its regulatory process.

POLICY

All submitted EAs are reviewed by an Environmental Reviewer. All claims of categorical exclusion are reviewed by a Quality Reviewer, except claims for the following application types, which are reviewed by an Environmental Reviewer: NDAs for new molecular entities (NMEs); NDAs or NDA supplements to such applications for drugs with possible estrogenic, androgenic, and thyroid pathway activity that request a categorical exclusion at 21 CFR §

25.31(b); and applications (i.e., ANDAs, NDAs, BLAs) or supplements to such applications for drugs or biologic products derived from cultivated plants or animals.

RESPONSIBILITIES

The Regulatory Business Project Manager (RBPM) will:

- Based upon input from the Application Technical Lead, or the Quality Reviewer, notify the Environmental Team at CDER.EA.Team@fda.hhs.gov that a reviewer is required for either (1) a submitted EA or (2) a claim of categorical exclusion for the following application types:

    - NDAs for NMEs.
    - NDAs or sNDAs for drugs with possible estrogenic, androgenic, and thyroid pathway activity that request a claim of categorical exclusion at 21 CFR § 25.31(b).
    - Applications, or supplements to applications, for drugs or biologic products derived from cultivated plants or animals.

- Add a Panorama task following current procedures and assign the task to the reviewer selected in response to the previous bullet.

The Environmental Reviewer will:

- Notify the RBPM of the selected reviewer for EAs or claims of categorical exclusion, as listed above.
- Review all submitted EAs.
- Review claims of categorical exclusion for the application types noted above for RBPMs, and request additional information from the applicant, as needed, to substantiate the claim of categorical exclusion (e.g., sales volumes, confirmation of cultivated plant status).
- For claims of categorical exclusion that are listed in the previous bullet and that require minimal review:

    - Request the Quality Reviewer to document the acceptance of a claim of categorical exclusion in the Drug Product Quality Review.
    - Provide appropriate acceptance statements to the Quality Reviewer for inclusion.

- Respond to questions about environmental reviews of EAs and claims of categorical exclusion from Quality Reviewers and others in a timely fashion.

The Quality Reviewer will:

- Review claims of categorical exclusion for the following application types, except as noted above:

  - INDs.
  - BLAs and sBLAs.
  - NDAs and sNDAs.
  - ANDAs and sANDAs.

- Request additional information from the applicant, as needed, to substantiate the claim of categorical exclusion (e.g., sales volumes).
- Request the statement of no extraordinary circumstances, if it is not included.
- Document in the quality review the acceptance of a claim of categorical exclusion, except for those reviewed by the Environmental Team.
- When requested by the Environmental Team, document in the Drug Product Quality Review the acceptance of a claim of categorical exclusion and include additional documentation/language as provided by the Environmental Reviewer.
- During IND development, inform the applicant of the need to contact the Environmental Team about environmental requirements for the following application types:

  - NDAs for NME.
  - NDAs and sNDAs for drugs with possible estrogenic, androgenic, and thyroid pathway activity—refer the applicant to the March 2016, guidance for industry *Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity*.[1]
  - ANDAs, sANDAs, NDAs, sNDAs, BLAs, and sBLAs for drug substances or precursors derived from non-cultivated ("wild") plant or animal sources—refer the applicant to the July 1998 guidance for industry *Environmental Assessment of Human Drugs and Biologics Applications, Part III.C.3* and the December 2016 guidance for industry *Botanical Drug Development*.

Contact the Environmental Team at CDER.EA.Team@fda.hhs.gov if there are any questions on whether: (1) a claim of categorical exclusion is adequate; (2) additional information is required from the sponsor or applicant to support the claim; and (3) an EA is required for a drug derived from plant or animal sources.

[1] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

REFERENCES

1. NEPA, 42 U.S.C. section 4321 et seq.
2. CEQ Regulations, 40 CFR parts 1500 to 1508
3. Fish and Wildlife Service CITES Regulations, 50 CFR part 23
4. Fish and Wildlife Service ESA Regulations, 50 CFR part 17
5. FDA Environmental Regulations, 21 CFR part 25
6. Related FDA Regulations in 21 CFR 314.50(d)(1)(iii), 314.94(a)(9)(i) and 314.101(d)(4)
7. FDA guidance for industry *Environmental Assessment of Human Drugs and Biologics Applications*, July 1998
8. FDA guidance for industry *Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity*, March 2016
9. FDA guidance for industry *Botanical Drug Development*, December 2016

DEFINITIONS/ACRONYMS

- ANDA: Abbreviated new drug application
- sANDA: Supplement to an ANDA
- BLA: Biologics License Application
- sBLA: Supplement to a BLA
- Categorical Exclusion: Classes of actions ordinarily excluded from the requirement for an Environmental Assessment
- CEQ: Council on Environmental Quality
- CFR: Code of Federal Regulations
- CITES: Convention on International Trade in Endangered Species of Wild Fauna and Flora
- EA: Environmental Assessment
- EIC: Expected introduction concentration of the active moiety that can enter the environment due to use. The EIC is based on a 5-year marketing estimate.
- Environmental Reviewer: CDER/OPQ Environmental Team Reviewer
- ESA: Endangered Species Act
- IND: Investigational new drug application
- NME: New molecular entity
- NDA: New drug application
- sNDA: Supplement to an NDA
- NEPA: National Environmental Policy Act of 1969, as amended
- Parts per billion (ppb): One unit of chemical per 1,000,000,000 (10^9) units of medium (e.g., water) or organism (e.g., tissue) in which it is contained. For water, 1 µg/L; for tissue, 1 µg/kg or 1 ng/g.
- Quality Reviewer: Generally the CDER/OPQ Drug Product Quality Reviewer
- RBPM: Regulatory Business Project Manager (OPQ)

EFFECTIVE DATE

This MAPP is effective on October 10, 2017.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
03/06/03	Initial	n/a
10/10/17	Rev. 1	Updated the policy and responsibilities.
11/23/2022	n/a	Recertification, no changes

ATTACHMENT: FREQUENTLY ASKED QUESTIONS

Q1. What environmental information must be included in an application?

All applications (e.g., NDAs, ANDAs, INDs, BLAs, supplements) and petitions requesting Agency action require the submission of an EA or a claim of categorical exclusion. [21 CFR § 25.15(a)]

Q2. Where are EAs and claims of categorical exclusion located in the electronic common technical document (eCTD)?

EAs and claims of categorical exclusion are located in Module 1 Section 1.12.14 of the eCTD.

Q3. Is the lack of an EA or claim of categorical exclusion a "refuse to file" or "refuse to receive" issue?

Yes. FDA may refuse to file an NDA or BLA or receive an ANDA if the applicant fails to submit a claim of categorical exclusion or to submit an EA. Furthermore, FDA may refuse to file an NDA or BLA or receive an ANDA if the applicant fails to submit a complete EA or fails to provide sufficient information to establish that the requested action is subject to a categorical exclusion. [21 CFR §§ 25.15(a), 314.101(d)(4)].

Q4. What is a claim of categorical exclusion?

A claim of categorical exclusion is a statement made by the sponsor or applicant that its application falls within a category of actions that FDA has identified in its regulations as not having a significant effect on the quality of the environment. An application that qualifies for a claim of categorical exclusion ordinarily does not require the preparation of an EA. The categorical exclusions specific to CDER are listed in 21 CFR § 25.31.

Q5. What must be included in a claim of categorical exclusion?

The sponsor or applicant must include, at a minimum, the following statements in a claim of categorical exclusion:

- A statement that the action requested qualifies for a categorical exclusion (with a citation to the regulations for the specific categorical exclusion that is claimed).
- A statement that to the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an EA. [21 CFR § 25.15(d)]

Sample statement: The requested action qualifies for a categorical exclusion from the requirement to prepare an EA, per 21 CFR § 25.31(b), because the estimated concentration of the substance at the point of entry into the aquatic environment is

estimated to be below 1 part per billion. To the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an EA.

Q6. What are extraordinary circumstances?

FDA will require at least an EA for any specific action that ordinarily would be excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment. [21 CFR § 25.21] Some examples of extraordinary circumstances for human drugs are:

- The drug substance or drug substance intermediate is derived from plants or animals taken from the wild.
- Available data establish that at the expected level of exposure there is the potential for serious harm to the environment.
- There is potential for action that adversely affects (1) a species or the critical habitat of species determined under the ESA or CITES to be endangered or threatened, or (2) wild fauna or flora entitled to special protection under some other Federal law.

Other examples of extraordinary circumstances are provided in the guidance for industry on *Environmental Assessment of Human Drug and Biologics Applications, Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity*, and in 40 CFR §1508.27.

Q7. What is needed for a review of a claim of categorical exclusion?

The Quality Reviewer or Environmental Reviewer will use appropriate guidance to document the quality review that a claim of categorical exclusion was submitted in the appropriate format, and include a statement regarding the acceptance of the claim.

Q8. Are data or other information needed to support or justify the claim of categorical exclusion?

Generally, additional information is not required. However, an applicant or sponsor may decide to provide information (e.g., market estimates) to support its claim of categorical exclusion. There also may be situations in which the FDA requests additional information to establish that the categorical exclusion criteria have been met. For example, additional information is requested in a categorical exclusion claim when the drug substance or a drug substance intermediate is derived from plants or animals (see section III.C.3 of the guidance for industry on *Environmental Assessment of Human Drug and Biologics Applications)*. Another example is when the sponsor has information indicating that a drug has or may have estrogenic, androgenic, or thyroid activity and the applicant requests a claim of categorical exclusion at 21 CFR § 25.31(b) (see *Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity*).

If the Quality Reviewer has any concerns that a claim of categorical exclusion may not be appropriate or should be further justified, contact the Environmental Team before contacting the sponsor or applicant.

Q9. When is an EA required?

The need for an EA depends on the specific circumstances of each application. The most common situations when an EA is required are when:

- A claim of categorical exclusion is found to be unacceptable.
- The application is of the type that will result in an increase in the amount of drug entering the environment and the EIC is 1 ppb or greater. See Appendix A and B of the guidance for industry on *Environmental Assessment of Human Drug and Biologics Applications* for information on actions that are considered likely to increase use or not increase use of the drug.
- The drug substance or drug substance precursor is derived from plants or animals taken from the wild. FDA intends to examine closely proposed actions for FDA-regulated articles obtained from fauna and flora and will require an EA in any instance in which it appears that the action may jeopardize the continued existence of a species. EAs could be submitted in the original application or supplemental applications relating to changes in biomass source or conditions detailed in a previous EA (e.g., amount, method, oversight, or location of harvesting).
- Drugs that have or may have estrogenic, androgenic, or thyroid activity also might need an EA (per *Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity*).

Q10. Is it possible that an EA will be required for a supplement to an approved application even though the original application or a previous supplement qualified for a categorical exclusion from the requirement to prepare an EA?

Yes. Each application submission is judged independently to determine whether an EA or categorical exclusion is appropriate. For example, an original NDA may have qualified for a categorical exclusion under 21 CFR § 25.31(b). However, increased use of the drug due, for example, to the addition of a new patient population may lead to an EIC > 1 ppb, resulting in the submission of an EA in an efficacy supplement.

Q11. What should be done if an EA is submitted, but the action appears to qualify for a categorical exclusion?

The Quality Reviewer should discuss the issues with the Environmental Team to determine whether the EA should be sent to them for review or whether the applicant should be contacted about the submission. After discussion between FDA and the applicant, the applicant could decide to replace its EA with a claim of categorical exclusion.

Q12. What should be done if an EA, instead of a claim of categorical exclusion, is assigned to the Quality Reviewer?

After discussion with the Environmental Team, the Quality Reviewer should request the RBPM to assign an EA task to the Environmental Reviewer.