OFFICE OF PHARMACEUTICAL SCIENCE

Environmental Assessments

CONTENTS

PURPOSE

- This MAPP summarizes policies and procedures for the receipt of environmental information in new drug applications (NDAs), abbreviated new drug applications (ANDAs), and investigational new drug applications (INDs), or supplements to these applications, and outlines the responsibilities of the chemistry 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 approving certain drug product applications as part of its regulatory process.

REFERENCES

- NEPA, 42 U.S.C. section 4321 *et seq*.
- CEQ Regulations, 40 CFR parts 1500 to 1508
- Fish and Wildlife Service CITES Regulations, 50 CFR part 23
- Fish and Wildlife Service ESA Regulations, 50 CFR part 17
- FDA Environmental Regulations, 21 CFR part 25
- Related FDA Regulations in 21 CFR 314.50(d)(1)(iii), 314.94(a)(9)(i) and 314.101(d)(4)
- FDA guidance for industry on *Environmental Assessment of Human Drugs and Biologics Applications*

DEFINITIONS AND ACRONYMS

- **ANDA**: Abbreviated new drug application
- **CDER**: Center for Drug Evaluation and Research
- **CEQ**: Council on Environmental Quality
- **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.
- **ESA**: Endangered Species Act
- **IND**: Investigational new drug application
- **NDA**: New drug application
- **NEPA**: National Environmental Policy Act of 1969, as amended
- **Part 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.
- **You**: Chemistry Reviewer

POLICY

- A request for categorical exclusion from the requirement to submit an environmental assessment (EA) will be evaluated by the chemistry reviewer and, when appropriate, referred to the EA staff. All EAs are to be evaluated by the EA staff.

RESPONSIBILITIES

- The Chemistry Reviewer will:

  Alert sponsors or applicants to the EA requirements as needed. For example, if during an IND meeting the sponsor indicates an intention to use a drug substance derived from plants taken from the wild as an ingredient in a commercial product marketed under an NDA, the sponsor should be advised that an EA would be required.

  Ensure that any EAs submitted are sent to the EA staff for a timely review.

  Document in the chemistry review the acceptance of a claim of categorical exclusion.

  Consult the EA staff if there are any questions on whether (1) an EA that has been submitted is needed, (2) a claim of categorical exclusion is appropriate or additional information is needed from the sponsor or applicant to support its claim, (3) an EA would be required for an application involving the use of plants or animals.

- The EA Staff will:

  Review all EAs submitted.

Respond to questions from chemistry reviewers and others in a timely fashion.

FREQUENTLY ASKED QUESTIONS (FAQS) BY CHEMISTRY REVIEWERS

Q1 What environmental information must be included in an application?

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

Q2 Is an EA or claim of categorical exclusion a "refuse to file" issue?

Yes. FDA may refuse to file an NDA or receive an ANDA if the applicant fails to (1) request a categorical exclusion or (2) submit an EA. Furthermore, FDA may refuse to file an NDA 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 § 314.101(d)(4)]

Q3 What is a categorical exclusion claim?

A categorical exclusion claim is a statement 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 human environment. The categorical exclusions specific to CDER are listed in 21 CFR § 25.31.

Q4 What must be included in a categorical exclusion claim?

The categorical exclusion claim must include statements by the sponsor or applicant that:

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

Sample statement: The requested action, approval of NDA 00-000, qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR § 25.31(b). To the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an EA.

Q5 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 intermediate or drug substance 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* and in 40 CFR §1508.27.

Q6 What type of chemistry review is needed for a categorical exclusion claim?

You should document in the chemistry review that a categorical exclusion in the appropriate format was submitted, and include a positive statement regarding the acceptance of the categorical exclusion claim.

Sample statements:

- A categorical exclusion has been submitted under 21 CFR § 25.31(b). The applicant states that to the applicant's knowledge, no extraordinary circumstances exist. The drug substance and intermediates are not derived from plants or animals taken from the wild. There is no information indicating that additional environmental information is warranted. The claim of categorical exclusion is accepted.

- A categorical exclusion has been submitted under 21 CFR § 25.31(c). The applicant states that to the applicant's knowledge, no extraordinary circumstances exist. Approval of this naturally occurring product is not expected to significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. There is no information that indicates extraordinary circumstances exist that would warrant the submission of additional environmental information. The categorical exclusion claim is accepted.

Q7 Are data or other information needed to support or justify the categorical exclusion claim?

Generally, additional information is not requested. However, an applicant or sponsor may voluntarily decide to provide information (e.g., market estimates) to support its categorical exclusion claim. There 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*).

If you have any concerns that a categorical exclusion claim may not be appropriate or should be further justified, you should consult the EA staff before contacting the sponsor or applicant.

Q8 When is an environmental assessment needed?

The need for an EA depends on the specific circumstances of each application.

The two most frequent situations when an EA is submitted are:

- 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 a drug substance intermediate is derived from plants or animals taken from the wild. 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).

Q9 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 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 may lead to an EIC > 1 ppb, resulting in the submission of an EA in an efficacy supplement.

Q10 What should be done if an environmental assessment is submitted, but the action appears to qualify for a categorical exclusion?

You should discuss the issues with the EA staff 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 categorical exclusion claim.

Q11 What should be done if an EA is submitted and it needs to be reviewed?

The EA and a "Request for Consultation" should be sent to the EA staff as soon as possible (e.g., before the 45-day meeting).

EFFECTIVE DATE

This MAPP is effective upon date of publication.