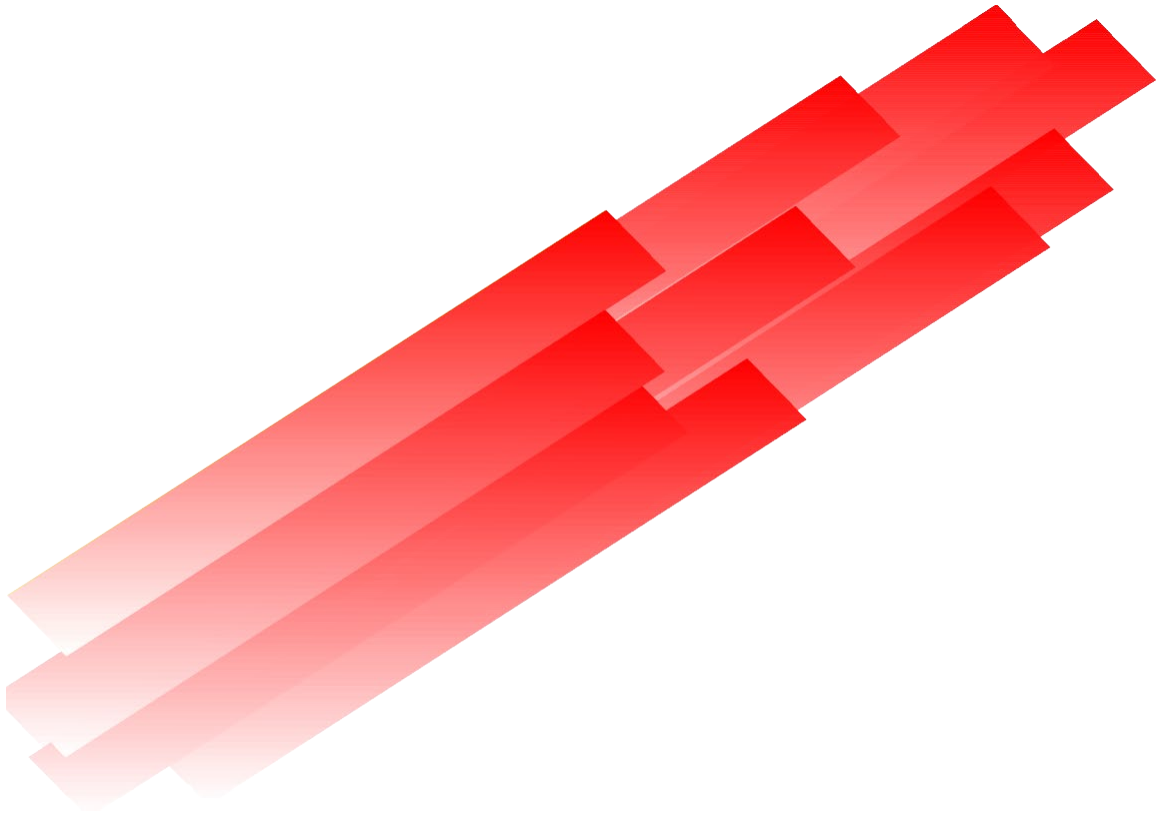
Guidance for Industry

Environmental Assessment of Human Drug and Biologics Applications



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
July 1998
CMC 6
Revision 1

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Copies of this guidance are available from the Office of Training and Communications, Division of Communications Management, Drug Information Branch, HFD-210, 5600 Fishers Lane, Rockville, MD 20857 (Phone 301-827-4573) or from the Internet at http://www.fda.gov/cder/guidance/index.htm.

Copies also are available from the Office of Communication, Training and Manufacturers Assistance, HFM-40, CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448, or from the Internet at http://www.fda.gov/cber/guidelines.htm. Copies also may be obtained by fax from 1-888-CBERFAX or 301-827-3844 or from Voice Information at 800-835-4709 or 301-827-1800.

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I. INTRODUCTION

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impacts of their actions and to ensure that the interested and affected public is informed of environmental analyses. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impacts of approving drug and biologics applications as an integral part of its regulatory process. FDA's regulations in 21 CFR part 25 specify that environmental assessments (EAs) must be submitted as part of certain new drug applications (NDAs), abbreviated applications, applications for marketing approval of a biologic product, supplements to such applications, investigational new drug applications (INDs) and for various other actions (see 21 CFR 25.20), unless the action qualifies for categorical exclusion.

Under the President's reinventing government (REGO) initiatives, announced in April 1995, FDA reevaluated and revised its environmental regulations to reduce the number of EAs required to be submitted by industry and, consequently, the number of findings of no significant impact (FONSIs) prepared by the Agency under NEPA. FDA issued for public comment a notice of proposed rulemaking on April 3, 1996 (61 FR 14922) (republished May 1, 1996 (61 FR 19476)), that proposed additional categorical exclusions for those actions that have been identified as normally not having a significant effect, individually or cumulatively, on the quality of the human environment. The final rule was published on July 29, 1997 (62 FR 40569), and became effective August 28, 1997. All applications or petitions requesting Agency action (e.g., NDAs, abbreviated new drug applications (ANDAs), INDs, biologics license applications (BLAs), supplements to such applications) must be accompanied by either an EA or a claim of categorical exclusion. Failure to provide (1) a claim of categorical exclusion or (2) an adequate EA, is sufficient grounds for ***refusing to file or approve*** the application (21 CFR 314.101(d)(4), 601.2(a) and (c), and 25.15(a)). An EA that is adequate for filing is one that addresses the relevant environmental issues. An EA adequate for approval is one that contains sufficient information to enable the Agency to determine whether the proposed action may affect significantly the quality of the human environment. This guidance provides information on when an EA should be submitted; it also makes recommendations on how to prepare EAs for submission of drug or biologics applications to the Center for Drug Evaluation and Research (CDER) and the Center for

[1] This guidance has been prepared under the direction of the Chemistry Manufacturing Controls Coordinating Committee, Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on environmental assessments. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Biologics Evaluation and Research (CBER). Topics covered include (1) when categorical exclusions apply, (2) when to submit an EA, (3) the content and format of EAs, (4) specific guidance for the environmental issues that are most likely to be associated with human drugs and biologics, (5) test methods, (6) an applicant's treatment of confidential information submitted in support of an EA, and (7) master files for drugs and biologics.

This guidance, which is based on the July 1997 final rule, will remain in effect until superseded by new regulations or new guidance. The guidance is intended to supersede CDER's *Guidance for Industry For the Submission of an Environmental Assessment in Human Drug Applications and Supplements,* which was published in November 1995. Information in this guidance, along with information in the Code of Federal Regulations (CFR) at 21 CFR part 25 and 40 CFR parts 1500-1508 and the FDA *Environmental Assessment Technical Handbook* (NTIS Publication Number PB 87 175345/AS), which provides information on acceptable test methods, represents the core information available from CDER and CBER to assist industry in preparing an EA.

II. WHAT TYPES OF ACTIONS ARE SUBJECT TO CATEGORICAL EXCLUSION?

Certain classes of actions are subject to categorical exclusion and, therefore, ordinarily do not require the preparation of an EA because, as a class, these actions, individually or cumulatively, do not significantly affect the quality of the human environment (21 CFR 25.5(c)). However, as required under 21 CFR 25.21 and 40 CFR 1508.4, 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.[2] See section III.C for additional information regarding extraordinary circumstances.

Submissions to CDER or CBER that ordinarily are excluded categorically under the regulations include actions on (1) NDAs, abbreviated applications, applications for marketing approval of a biologic product, and supplements to such applications if FDA's approval of the application does not increase the use of the active moiety; (2) NDAs, abbreviated applications, and supplements to such applications if FDA's approval of the application increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb); (3) NDAs, abbreviated applications, applications for marketing approval of a biologic product, and supplements to such applications for substances that occur naturally in the environment when the approval of the application does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment; (4) INDs; and (5) applications for marketing approval of a biologic product for transfusable human blood or blood components and plasma. An applicant is eligible

[2] Regulations would require an EIS (environmental impact statement) when "evaluation of data or information in an EA or otherwise available to the agency leads to a finding by the responsible agency official that a proposed action may significantly affect the quality of the human environment (21 CFR 25.22(b)).

to file a claim of categorical exclusion from the requirement to submit an EA if the action meets the criteria of at least one categorical exclusion.

A person submitting an application or petition of a type subject to categorical exclusion under 21 CFR 25.31 is not required to submit an EA if the person states that the action requested qualifies for categorical exclusion, citing the particular categorical exclusion that is claimed, and states that to the applicant's knowledge, no extraordinary circumstances exist (21 CFR 25.15(d)). An applicant ordinarily need not provide data to demonstrate that the action qualifies for categorical exclusion. CDER and CBER can rely on other information submitted in an application to evaluate the appropriateness of a claim for categorical exclusion. In the limited instances when it may be necessary, CDER or CBER will request additional information as needed to establish to their satisfaction that the criteria for categorical exclusion have been met.

III. WHEN IS AN EA REQUIRED?

Preparation of an environmental assessment ordinarily is required unless the proposed action qualifies for an exclusion under 21 CFR 25.30 or 25.31. An EA would also be required if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment (21 CFR 25.21).

Detailed information is provided below for the most common situations when actions would not qualify for categorical exclusion.

A. NDAs, Abbreviated Applications, and Supplements

Note: Section 1, below, should be used to assess increased use of a biological product as referenced in 21 CFR 25.31(a). Section 2 does not apply to biologics license applications (BLAs) because BLAs are not included in the categorical exclusion on which this section is based (21 CFR 25.31(b)). BLAs should be evaluated for whether they are eligible for categorical exclusion using 21 CFR 25.31(a) or (c) or other appropriate categorical exclusions found in 21 CFR 25.30 and 25.31.

NDAs, abbreviated applications, and supplements to such applications would not qualify for categorical exclusion if FDA's approval of the application increases the use of the active moiety ***and*** the estimated concentration of the substance at the point of entry into the aquatic environment will be 1 ppb or greater.

1. Increased Use

Increased use of an active moiety may occur if the drug will be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect, or if the drug is a new molecular entity. The term *use* also encompasses disposal of FDA-regulated articles by consumers.

Attachment A contains examples of actions that would not be considered to increase the use of a drug and Attachment B contains examples of actions that would be considered to increase the use of a drug or biologic. These lists are not inclusive. An applicant is encouraged to contact the appropriate Center if any questions arise as to whether a particular action is considered to increase the use of a drug or biologic.

2. Estimating the Concentration of a Substance at the Point of Entry into the Aquatic Environment

The expected introduction concentration (EIC) of an active moiety into the aquatic environment should be calculated as follows:

EIC-Aquatic (ppb) = A x B x C x D where

A = kg/year produced for direct use (as active moiety)
B = 1/liters per day entering POTWs*
C = year/365 days
D = 10^9 μg/kg (conversion factor)

* 1.214 x 10^{11} liters per day entering publicly owned treatment works (POTWs), Source: *1996 Needs Survey, Report to Congress.* Information regarding the *Needs Survey* is available on the Internet at http://www.epa.gov/owm. It is updated periodically.

This calculation assumes:

- All drug products produced in a year are used and enter the publicly owned treatment works (POTW) system.

- Drug product usage occurs throughout the United States in proportion to the population and amount of waste water generated.

- There is no metabolism.

The estimate of the kilogram/year active moiety should be based on or include (1) the highest quantity of the active moiety expected to be produced for direct use in any of the next five years. *Produced for direct use* means the quantity intended for use in humans during a given year (i.e., excludes any quantity produced for inventory buildup), (2) the quantity used in all dosage forms and strengths included in the application, and (3) the quantity used in an applicant's related applications. Related applications include those for other dosage forms using the same active moiety and for products using different forms of the active moiety (e.g., level of hydration, salt, free acid/base). All concentrations should be reported as the

concentration of active moiety, rather than the salt or complex.

The calculation of the expected introduction concentration (EIC) of an active moiety entering into the aquatic environment from patient use can consider the extent of metabolism of the active moiety to less pharmacologically active or inactive compounds, if that information is available. The pharmacological activity of metabolites relative to the active moiety should be considered when calculating the EIC. The weighted contribution of the metabolite to the EIC should be calculated (e.g., kg/year active moiety x 10% x 0.5 for a metabolite found at a level of 10% and that has half the pharmacological activity of the active moiety). If the pharmacological activity of the metabolite is unknown, it can be assumed to be the same as the active moiety.

An alternative calculation should be used if the drug product is intended for use in a specific geographic location (e.g., use an alternative value for the amount of liters per day entering POTWs — term B in the EIC calculation above). Moreover, if an alternative calculation is used to estimate localized use, or for any other reason, the calculation and the source and basis for the alternative calculation should be provided when filing an EA or a claim of categorical exclusion and would be subject to review.

B. Applications for Substances that Occur Naturally in the Environment

NDAs, abbreviated applications, applications for marketing approval of a biologic product and supplements to such applications for substances that occur naturally in the environment would not qualify for categorical exclusion under 21 CFR 25.31(c) when FDA's approval of the application alters significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. This might be the case when the use and disposal occur in a geographic area where the substance does not naturally occur. However, the application may be eligible for a categorical exclusion under other provisions in 21 CFR 25.31.

In addition to drug and biologic products derived from natural sources or from biological systems, substances can be considered naturally occurring even if they are chemically synthesized. The Agency will consider the form in which the FDA-regulated article will exist in the environment when determining whether the drug or biologic is a naturally occurring substance. For example, a modified active moiety (e.g., salt) that does not occur naturally could be considered a naturally occurring substance if it is established that, in vivo and in the environment, the active moiety exists in a form that is found naturally.

Biological and biotechnological products will be similarly evaluated. For example, a protein or DNA comprising naturally occurring amino acids or nucleosides, but having a sequence different from that of a naturally occurring substance, will normally qualify as a

naturally occurring substance after consideration of metabolism. The same principle would apply to synthetic peptides and oligonucleotides and living and dead cells and organisms. CDER and CBER may rely on other information submitted in an application (e.g., information about metabolism, excretion, and stability; viability (if applicable); and physical and/or chemical characteristics of the product) in determining whether the FDA-regulated article would be considered a naturally occurring substance.

CDER and CBER will evaluate on a case-by-case basis the appropriateness of categorical exclusions claiming that the quantity of the naturally occurring substance that is expected to enter the environment as a result of an action will not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

C. Extraordinary Circumstances

As stated in 21 CFR 25.21 and 40 CFR 1508.4, FDA will require at least an EA for any specific action that ordinarily would be categorically excluded if extraordinary circumstances indicate that the specific proposed action could significantly affect the quality of the human environment. Extraordinary circumstance can be shown by data available either to the Agency or the applicant and can be based on the production, use, or disposal from use of the FDA-regulated article. Data available to the Agency can include public information, information submitted in the application, and data available to the Agency on the same or similar products.

1. Actions for which available data establish that there is a potential for serious harm to the environment at the expected level of exposure.

FDA considers harm to the environment to include not only toxicity to environmental organisms but also environmental effects other than toxicity, such as lasting effects on ecological community dynamics.

2. Actions that adversely affect a species or the critical habitat of a species determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora to be endangered or threatened, or wild fauna or flora that are entitled to special protection under some other Federal law.

Actions that adversely affect a species or the critical habitat of a species determined under the Endangered Species Act to be endangered or threatened, wild fauna or flora listed in the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), or wild fauna or flora that are entitled to special protection under some other Federal law or international treaty to which the United States is a party would be considered an extraordinary circumstance, and an EA should be submitted unless there are specific exemptions relating to the

pharmaceutical substances or FDA action. An example of an exception would be when a species is afforded special protection under Federal law or international treaty, but the pharmaceutical is derived only from nonwild specimens. If nonwild specimens are exempted from Federal law or treaty, the action would be eligible for categorical exclusion as indicated in section III.C.3.a. Both direct effects (e.g., pharmaceuticals derived from fauna or flora, see section III.C.3) and indirect effects (e.g., adverse effects from manufacturing site emissions) should be considered.

Under the U.S. Endangered Species Act (ESA), Congress declared, "[T]he United States has pledged itself as a sovereign state in the international community to conserve to the extent practicable the various species of fish or wildlife and plants facing extinction, pursuant to the Convention on International Trade in Endangered Species of Wild Fauna and Flora" (16 U.S.C. 1531(a)(4)(F)). Identification as an endangered or threatened species does not preclude the use of such fauna or flora. However, under the ESA, if a species has been determined to be endangered or threatened, a Federal agency is required to consult with the Secretary of Interior or the Secretary of Commerce to ensure that the agency's actions are not likely to jeopardize the continued existence of endangered or threatened species or their critical habitats (16 U.S.C. 1536).

3. Use of Fauna or Flora

FDA intends to examine closely the proposed actions for FDA-regulated articles obtained from fauna and flora and will use the extraordinary circumstances provision to require an EA in any instance in which it appears from an examination of the proposed action that the action may jeopardize the continued existence of a species. The following sections discuss CDER's and CBER's current position on when the use of fauna or flora normally would constitute an extraordinary circumstance for which an EA should be submitted to support the application.[3]

a. Cultivated Specimens

Actions involving drug or biologic products derived from cultivated plants (e.g., plantation, nursery stock) or bred or domestic animals (e.g., laboratory breed, cows, pigs) are not normally considered an extraordinary circumstance that would require an EA for an action that is normally categorically excluded (see section III.C.2 for a possible exception).

b. Wild Specimens

[3] FDA may clarify the environmental information that must be submitted to the Agency in marketing applications for specific drug or biologic products derived from plants or animals (e.g., paclitaxel, 61 FR 58694).

i. NDAs, abbreviated applications, applications for marketing approval of a biologic product, or certain supplements to such applications.

NDAs, abbreviated applications and applications for marketing approval of a biologic product where the drug or biologic product is derived from plants or animals taken from the wild, supplements to such applications that relate to changes in the source of the wild biomass (e.g., species, geographic region where biomass is obtained), or supplements to such applications that are considered to increase the use of an active moiety or biologic substance (see Attachment B) and which will cause more harvesting than what was described in the original EA would be considered an extraordinary circumstance, and an EA should be submitted.

ii. INDs

INDs generally involve relatively small quantities of a drug or biologic product and treatment of a limited number of patients. Many INDs never result in the filing of an NDA or application for marketing approval of a biologic product, which would allow for the wide-spread commercial sale of the product. CDER and CBER will evaluate INDs on a case-by-case basis where the drug or biologic product is derived from wild plants or animals to determine whether the extraordinary circumstance provision in 21 CFR 25.21 is invoked.

To facilitate Center review, when submitting a claim of categorical exclusion for actions where the drug or biologic product is derived from plants or animals, CDER and CBER request that the applicant provide the following information with the claim, or specifically identify where the information can be located (e.g., page number of application): (1) biological identification (i.e., common names, synonyms, variety, species, genus and family); (2) a statement as to whether wild or cultivated specimens are used; (3) the geographic region (e.g., country, state, province) where the biomass is obtained; and (4) a statement indicating whether the species is (a) determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened, (b) entitled to special protection under some other Federal law or international treaty to which the United States is a party, or (c) the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or is entitled to

special protection under some other Federal law or international treaty to which the United States is a party. CDER and CBER will use this information to evaluate whether the claim of categorical exclusion is appropriate.

4. Production and Disposal Sites

FDA has found that regulated articles produced and disposed of in compliance with all applicable emission requirements do not significantly affect the environment and has determined it is unnecessary to review a company's compliance with Federal, State, and local environmental laws. In addition, both CDER and CBER routinely require as part of their safety evaluations that live organisms be inactivated following production and prior to release into the environment if there is a reasonable possibility that the living system may be harmful to the environment. Therefore, CDER and CBER will not routinely request submission of manufacturing and disposal information in an EA. However, if information available to the Agency or the applicant establishes that the general or specific emission requirements promulgated by Federal, State, or local environmental protection agencies do not address unique emission circumstances and the emissions may harm the environment, this would be sufficient grounds for requesting manufacturing or disposal information in an EA. Actions that threaten a violation of Federal, State, or local law or requirements imposed for the protection of the environment may constitute a significant impact (40 CFR 1508.27(b)(10)).

5. Significant Effects as Defined in 40 CFR 1508.27

The Council on Environmental Quality has provided a definition of "significantly" to aid in determining if an action may significantly affect the quality of the human environment. These examples should be considered when evaluating whether extraordinary circumstances exist that may warrant submission of at least an EA (See Attachment C).

IV. PREPARING AN EA FOR SUBMISSION TO CDER or CBER

A. Content and Format

This section describes the basic information that should be submitted in an EA if an EA is required. Attachment D contains an outline of the format for an EA. Alternative formats may be used, but the applicant should recognize that use of a standard format, such as described in this guidance, promotes efficiency in the review process.

1. Date

The EA should include the date the EA was originally prepared and the date(s) of any subsequent amendments.

2. Name of Applicant or Petitioner

The EA should identify the applicant who is submitting the application.

3. Address

The EA should contain the address where all correspondence is to be directed.

4. Description of Proposed Action

a. Requested Approval

The description of the requested approval should include the drug or biologic application number (if available), the drug or biologic product name, the dosage form and strength, and a brief description of the product packaging. For example, "XYZ Pharmaceuticals has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (established name), 250 mg and 500 mg, packaged in OHDPE bottles. An EA has been submitted pursuant to 21 CFR part 25."

b. Need for Action

The EA should briefly describe the drug's or biologic's intended uses in the diagnosis, cure, mitigation, treatment, or prevention of disease.

c. Locations of Use

The EA should identify the location(s) where the product will be used. Depending on the type of product and its use, the locations of use are typically identified as hospitals, clinics and/or patients in their homes. If use is expected to be concentrated in a particular geographic region, this fact should be included.

d. Disposal Sites

Unless other disposal methods by the end user are anticipated, it is sufficient to state that at U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures and/or that in the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and

recycling, although minimal quantities of the unused drug could be disposed of in the sewer system.

5. Identification of Substances that are the Subject the Proposed Action

The EA should contain information that allows for the accurate location of data about the substance in the scientific literature and for identification of closely related compounds. At a minimum, the information listed below should be provided, if available. For many biological products, format items 5.a.iii, b, c, and d will not apply. Other information, such as the international nonproprietary name (INN) or nonsystematic or semisystematic chemical names should be included if deemed useful in the identification of the compounds.

Usually this information need only be provided for the drug or biologic substance, but the same information also should be provided for the form of the active ingredient in the drug or biologic product if it is different from the drug or biologic substance (e.g., a salt formed in situ from a free base) or for a pharmacologically active related substance formed by conversion from a pharmacologically inactive parent compound (e.g., a prodrug product is converted to the pharmacologically active form).

a. Nomenclature

i. Established Name (U.S. Adopted Name-USAN)

ii. Brand/Proprietary Name/Tradename

iii. Chemical Names or Genus/Species of Biologic Product (e.g., virus)

- Chemical Abstracts (CA) Index Name (inverted form)

- Systematic Chemical Name (uninverted form)

b. Chemical Abstracts Service (CAS) registration number

c. Molecular Formula

d. Molecular Weight

e. Structural (graphic) Formula/Amino Acid Sequence

6. Environmental Issues

The type of information provided will vary depending on the environmental issues associated with the particular action. In general, the EA should include a succinct description of the environmental issues. The affected environment and the environmental effects and their significance should be discussed. Data and analyses to support the discussions should be provided as appropriate. Specific guidance is provided in section IV.B for the environmental issues that are most likely to be associated with human drugs and biologics. For environmental issues not specifically addressed in section IV.B (e.g., those included in sections III.C.4 and 5), applicants are encouraged to consult the appropriate Center prior to preparing the EA.

7. Mitigation Measures

Describe measures taken to avoid or mitigate any potential adverse environmental effects associated with the proposed action. If no adverse environmental effects have been identified, it should be so stated and indicated that, therefore, no mitigation measures are needed. See section IV.B.2.b for additional information regarding the discussion of mitigation measures for actions involving fauna and flora.

8. Alternatives to the Proposed Action

If no potential adverse environmental effects have been identified for the proposed action, the EA should state this. If potential adverse environmental effects have been identified for the proposed action, the EA "shall discuss any reasonable alternative course of action that offers less environmental risk or that is environmentally preferable to the proposed actions" (21 CFR 25.40(a)). The discussion should include the no-action alternative and measures that FDA or another government agency could undertake as well as those the applicant or petitioner would undertake. The EA should include a description of those alternatives that will enhance the quality of the environment and avoid some or all of the adverse environmental effects of the proposed action. The environmental benefits and risks of the proposed action and the environmental benefits and risks of each alternative should be discussed. See section IV.B.2.c for additional information regarding the discussion of alternatives for actions involving fauna and flora.

9. List of Preparers

The EA should include the name, job title, and qualifications (e.g., educational degrees) of those persons preparing the assessment and should identify any persons or agencies consulted. Contract testing laboratories should be included in the list of consultants, although this may be included in a confidential appendix. Curriculum vitae can be included in lieu of a description of an individual's

qualifications.

10. References

The EA should include a list of citations for all referenced material and standard test methods used in generating data in support of the EA. Copies of referenced articles that are not generally available and that are used to support specific claims in the EA document should be attached in a nonconfidential appendix.

11. Appendices

Both confidential and nonconfidential appendices can be included. See section IV.E for additional information about the treatment of confidential information. A list of the appendices should be included in the EA summary document with a designation of confidential or nonconfidential following each of the listings. Typically, the nonconfidential appendices include data summary tables and copies of referenced articles that are generally unavailable or that were used to support specific claims in the EA. Proprietary or confidential information, such as use estimates and test reports, should be included in the confidential appendices.

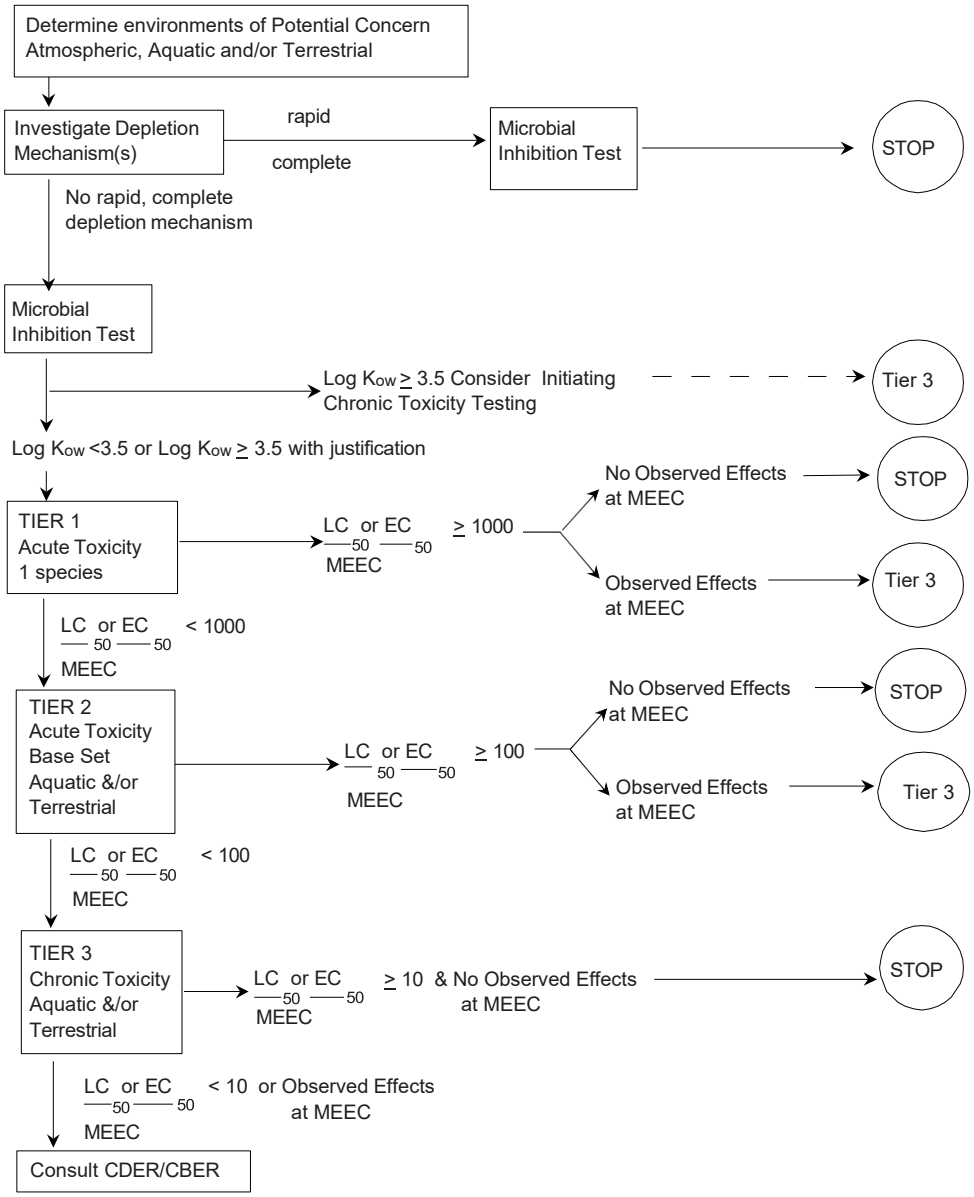
B. Specific Guidance — Environmental Issues

1. Assessing Toxicity to Environmental Organisms

If an EA is required, it normally should focus on characterizing the fate and effects of the compound of interest in the environment (1) when FDA's approval of the application increases the use of an active moiety and the estimated concentration of the active moiety at the point of entry into the aquatic environment is 1 ppb or greater (see section III.A); (2) when the substance occurs naturally in the environment and FDA's approval of the application alters significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment (see section III.B); or (3) in some cases, when data available to the Agency or applicant establish that at the expected level of exposure, there is the potential for serious harm to the environment (see section III.C.1). The provided information should focus on the fate and effects of the active moiety and/or structurally related substances (SRSs), rather than on excipients, for example.

The Centers encourage the use of a logical, tiered approach to testing so that adequate information is available to assess the potential environmental fate and effects of pharmaceuticals while minimizing the cost to industry. Figure 1 provides an illustration of a tiered approach. Alternative, scientifically justified approaches also can be used.

Figure 1
Tiered Approach to Fate and Effects Testing



Note: MEEC = EEC or EIC whichever is greater

Information submitted for fate and effects can include specific data generated on the test substance or relevant information on analogous compounds from the submitter or from peer-reviewed literature as appropriate. Actual experimental data regarding base parameters are generally preferable to computer modeling; however, in some circumstances computer modeling may be appropriate. FDA should be consulted if a company believes computer modeling is appropriate and wishes to use modeling in an EA.

a. Environmental Fate of Released Substances

i. Identification of Substances of Interest

The actual substances that will enter or exist in the environment (i.e., atmospheric, aquatic, terrestrial) can include the parent compound (i.e., drug or biologic substance) or SRSs such as the dissociated parent compound, metabolites, or degradants. The EA should list the drug or biologic substance and the predominant SRSs expected to enter or exist in the environment; provide the name, chemical structure and CAS number when possible; and provide a rationale for the decision as to which substance(s) will be studied. Predominant SRSs should be considered those greater than 10 percent of dose.

In most cases, fate (and effects) information should be provided on the parent (or active) drug or biologic substance, as representative of substances entering the environment. Such information is relevant to SRSs when the SRSs possess the same fundamental structure as the parent drug or biologic substance and are comparably or more polar. At a minimum, the EA should contain a discussion of the potential fate and effects of the predominant SRSs based on their structural differences and/or similarities to the parent compound (e.g., due to a functional group change, the metabolite should be more soluble than the parent compound, or the SRS is more polar). Computerized structure-activity relationship modeling programs may be useful in supporting extrapolation of fate and effects information from the parent (or active) drug or biologic substance to the SRS. Relevant available pharmacologic activity and toxicity information should be provided for the SRSs. Specific toxicity-activity information for SRSs may be included in a confidential appendix. Additional environmental information on a predominant SRS may be warranted, following consultation with the appropriate Center, if the fate of the compound is expected to differ from the parent compound, or there is an indication that the

SRSs effect on the environment would be substantially greater than from the parent drug or biologic substance.

ii. Physical and Chemical Characterization

The following tests should be conducted to determine if the compound is most likely to amass predominantly in aquatic, terrestrial, and/or atmospheric environments:

- Water Solubility
- Dissociation Constant(s)
- Octanol/Water Partition Coefficient
- Vapor Pressure or Henry's Law Constant

If there is a scientific basis for not performing a test, the justification should be included in the EA (e.g., water solubility was not determined because the compound is hydrolytically unstable). For a test compound that associates or dissociates in water, water solubility and the octanol/water partition coefficient may have to be determined at pH 5 and 9 as well as pH 7.

The octanol/water partition coefficient (K_{ow}) is an indicator of a nonionized compound's potential to adsorb to the organic fraction of soil, sediment, or biosolids (i.e., sludge) in addition to being an indicator of a compound's lipophilicity. It is not as good a predictor for inorganic chemicals, metal organic complexes, dissociating, ionic organic compounds, or compounds with other mitigating structural features such as molecular size. Further study of the sorption and/or desorption properties (K_{oc}) of a substance to biosolids should be considered if log K_{ow} is greater than 3 or other properties indicate that sorption or desorption may occur.

iii. Environmental Depletion Mechanisms

Depletion mechanisms should be investigated to determine if there is degradation of the compound in the environment(s) of interest. It is usually sufficient to provide basic supporting information that identifies the potential for a compound to be removed from the environment by a depletion mechanism (e.g., photolysis or hydrolysis based on information developed for analytical methods validation or from stability studies). It is unnecessary to go to

extraordinary effort to identify a depletion mechanism once the typical depletion mechanisms (i.e., hydrolysis, photolysis, biodegradation) have been investigated or to continue investigating other potential depletion mechanisms once one has been identified.

If the depletion mechanism is being used to reduce the expected introduction concentration or to eliminate effects testing, a formal, detailed analysis of the depletion mechanism should be provided (e.g., according to a standard test method, rate determination, analysis of expected exposure time in the environment).

Consideration should be given to the nature and extent of the degradation. If a rapid, complete depletion mechanism is identified (degradants are relatively simple, polar by-products), no testing to determine the environmental effects of the compound should be performed except for a microbial inhibition test or other appropriate test to assess the potential for the compound to disrupt waste treatment processes. Based on the estimated time prior to emission from a treatment facility, the following would be considered rapid depletion mechanisms:

Hydrolysis $t_{½}$ (pH 5-9):	:, 24 hours
Aerobic Biodegradation $t_{½}$:	:, 8 hours
Soil Biodegradation $t_{½}$:	:, 5 days

Direct and indirect photolysis, although significant under laboratory conditions, may not be as rapid a depletion mechanism in the environment due to significant variation in light intensity (e.g., related to weather, latitude, depth penetration) and duration of exposure. Efforts to characterize photolysis as a depletion mechanism should take these factors into consideration.

iv. Environmental Concentrations

Expected Introduction Concentration (EIC): The environmental introduction concentrations into those environments (i.e., aquatic, terrestrial, atmospheric) where the substance(s) of interest is most likely to amass (see section IV.B.1.a.ii) should be estimated. A method of calculating the expected introduction concentration of a substance into the aquatic environment is described in section III.A.2. The calculation of the expected introduction concentration (EIC) entering into the aquatic environment from patient use, in addition to considering metabolism as described in section III.A.1, may include consideration of the environmental depletion

mechanisms that occur in the waste treatment process (e.g., adsorption, degradation, hydrolysis), if the information is available (see section IV.B.1.a.iii).

Some drug or biologic substance and/or active moiety may enter the terrestrial environment when biosolids from waste water treatment facilities, which contain adsorbed material, are applied to land. Application of biosolids to land is subject to regulation by the Environmental Protection Agency (EPA) or an appropriate State authority. Biosolids are generally subjected to some form of aerobic or anaerobic digestion in the waste treatment facility. The EIC for the terrestrial compartment should be estimated if, based on the available physical or chemical properties of the compound, significant quantities of the active moiety are expected to adsorb to biosolids. The calculation used will depend on the typical treatment, disposal, and application processes. Currently, approximately 6.8 million tons of biosolids (dry basis) are generated per year with 54 percent of that quantity being applied to land. The remaining biosolids are incinerated, landfilled or disposed of by other means. Depletion mechanisms (e.g., biodegradation, hydrolysis) that occur in the waste treatment process can be considered when calculating the EIC for the terrestrial compartment, if the information is available. Additional information regarding land application of biosolids is available from EPA's Office of Wastewater Management (on the Internet at http://www.epa.gov/owm/bio.htm).

The concentration expected in the atmospheric compartment need not be routinely calculated for pharmaceutical products administered through inhalation because, for the majority of these, the active moiety or other compound of interest is not released into the air. However, the EIC should be considered for products that are released primarily into the air (e.g., medical gases).

CDER and CBER have defined *use* to encompass disposal of FDA-regulated articles by consumers. Normally, the EIC from disposal need not be calculated since the majority of pharmaceutical products will be totally consumed, and any residual waste will typically be disposed of in landfills or at incineration facilities that are regulated by the EPA or appropriate State agencies. These agencies have considered the environmental impacts from the operation of these facilities in their licensing process and require controls (e.g., scrubbers, lined landfills, migration tests) to limit the release of materials into the environment. The EIC for disposal

should be calculated if significant quantities of material are expected to be disposed of other than by landfill, incineration or other procedures regulated by the EPA or appropriate State agencies.

Expected Environmental Concentration (EEC): The expected environmental concentration (EEC), sometimes referred to as the *predicted environmental concentration* (PEC), is the concentration of the active moiety or other compound of interest that organisms would be exposed to in the environment (e.g., surface water) after consideration of, for example, spatial or temporal concentration or depletion factors such as dilution, degradation, sorption and/or bioaccumulation. Adjustments to the expected introduction concentration may be made, based on spatial and temporal concentration or depletion factors, to provide an expected environmental concentration. Supporting information and/or discussion should be provided to explain the factors used in calculating the expected environmental concentration. The concentration should be provided for each environmental compartment (aquatic, terrestrial, atmospheric) expected to be affected based on the physical and/or chemical characterization of the compound of interest. In the majority of cases, the EEC for the aquatic environment would be expected to be significantly less than the EIC for the aquatic environment due to dilution. Based on dilution factors for POTWs available from the EPA, applying a dilution factor of 10 to the EIC-aquatic to estimate the EEC-aquatic is normally appropriate.

v. Summary

A summary discussion of the environmental fate of the substance(s) of interest should be provided for each environmental compartment based on the information and data provided in the EA, and the environmental compartment(s) in which the substance is expected to predominantly amass should be identified. In some circumstances, transport between environmental compartments should be considered when determining the fate of the substance(s) of interest in the environment.

Aquatic Environment: In general, pharmaceutical substances are expected to enter predominantly into the aquatic environment and, therefore, the focus of any effects studies most likely will be on aquatic organisms. If the substance(s) of interest rapidly degrades (see section IV.B.1.a.iii) or adsorbs completely and irreversibly to

biosolids, then fate and effects in the aquatic environment should not usually be considered.

Terrestrial Environment: In general, substances enter the terrestrial environment predominantly from biosolids removed from waste water treatment plants that are subsequently applied to land. Therefore, effects on the terrestrial environment are more likely if a compound adsorbs to biosolids (see section IV.B.1.a.ii). Biosolids are generally subjected to some form of aerobic or anaerobic digestion in the waste treatment facility; only a fraction of the biosolids may be applied to land, while the remainder is incinerated or land filled. Fate and effects testing in the terrestrial environment should be considered if testing indicates that the substance(s) of interest will significantly adsorb to biosolids (e.g., K_{oc} ;„ 1000).

Atmospheric Environment: In general, substances that do not adsorb readily to soils, have a high vapor pressure, and have a low water solubility, are likely to volatilize significantly from the aquatic or terrestrial environments, although actual volatilization rates will depend on environmental conditions (e.g., dispersion away from the evaporation site) and on factors that can lessen or enhance the effective vapor pressure or behavior of the chemical at a liquid-air or solid-air interface. The atmospheric compartment may be of interest for medical gases. But, based on the polarity of the majority of compounds at relevant aquatic environmental conditions, it is unlikely that there would be substantive partitioning from the aquatic to the atmospheric environment for other pharmaceuticals. Any potential for a substance to volatilize and recycle into the aquatic or terrestrial environments should be discussed based on the information and data available for the substance.

b. Environmental Effects of Released Substances

Tiered approach to environmental effects testing (see below, Microbiological Inhibition Testing through Tier 3 Testing and Figure 1): If no rapid, complete depletion mechanism has been identified, it should be assumed that the compound will persist in the environment for some time and, therefore, the toxicity of the released substances to environmental organisms should be evaluated. The fate of the substance should be considered when designing the studies. For those compounds that enter the atmospheric environment, testing should be designed based on the extent to which the substance recycles into the aquatic or terrestrial environments. All toxicity test results for the drug or biologic substance

should be reported in terms of the quantity and/or concentration of the active moiety. When using this tiered approach to effects testing, it is important to design the test conditions appropriately so that a no-observed-effects concentration is determined.

Microbial Inhibition Testing: A microbial inhibition test or other appropriate test (e.g., respiration inhibition testing) should be performed to assess the substance(s) of interest's potential to inhibit microorganisms and subsequently disrupt waste treatment processes.

Assessment Factors: The assessment factors are intended to provide a consistent regulatory basis for determining when additional ecotoxicity testing should be performed (tiered approach). They are directly related to the amount of valid ecotoxicity data available. If the LC_{50} or EC_{50} or other appropriate test endpoint divided by the maximum expected environmental concentration (MEEC: EIC or EEC, whichever is greater) is less than the assessment factor, additional testing should be performed. The use of EC_{50} or test end point other than the LC_{50} should be limited to those test organisms for which the LC_{50} is not the test endpoint.

TEST TIER	ASSESSMENT FACTOR
1	1000 (see below)
2	100 (see below)
3	10 (see below)

Alternative scientifically justified approaches also can be used.

Tier 1 Testing: Acute ecotoxicity testing should be performed on a minimum of one suitable test organism (see base set for Tier 2 testing). If the EC_{50} or LC_{50} divided by the MEEC is greater than or equal to 1000, no further testing should be conducted unless sublethal effects are observed at the MEEC. If the EC_{50} or LC_{50} divided by the MEEC is less than 1000, Tier 2 testing should be performed. Sublethal effects (observed effects) at the MEEC indicate that chronic toxicity testing (Tier 3) should be performed. The use of the assessment factor of 100 could be used for Tier 1 testing if there is evidence (e.g., Tier 2 testing on a similar compound) to support that the single test organism used would be expected to be the most sensitive of the base set test organisms. If the compound is expected to partition to both the aquatic and terrestrial environments, usually testing of an aquatic test organism is sufficient since CDER has routinely observed lower toxicity results reported for aquatic test organisms as compared to terrestrial test organisms.

Tier 2 Testing: Acute ecotoxicity testing should be performed on the minimum base set of aquatic and/or terrestrial organisms. The aquatic base set usually consists of (1) a fish acute toxicity test, (2) an aquatic invertebrate acute toxicity test, and (3) an algal species bioassay. The terrestrial base set usually consists of (1) plant early growth tests, (2) earthworm toxicity tests, and (3) soil microbial toxicity tests. Usually only an earthworm toxicity study is indicated if the substance binds tightly to soil. A rodent acute toxicity is not included in the terrestrial base set since there is usually a significant quantity of mammalian (e.g., mouse, rat, dog, monkey, human) toxicity testing performed, both acute and chronic, to support the underlying applicacton and to demonstrate the safety of the drug or biologic product. Consultation with CDER or CBER is suggested prior to initiating any terrestrial studies.

If the EC_{50} or LC_{50} for the most sensitive organism in the base set divided by the MEEC is greater than or equal to 100, no further testing should be conducted unless sublethal effects are observed at the MEEC. If the EC_{50} or LC_{50} divided by the MEEC is less than 100, Tier 3 testing should be performed. Sublethal effects (observed effects) at the MEEC indicate that chronic toxicity testing (Tier 3) should be performed.

Tier 3 Testing: Chronic toxicity testing should be considered if the compound has the potential to bioaccumulate or bioconcentrate, if indicated based on Tier 1 and/or Tier 2 testing, or if there are other indications that the compound undergoes biotransformation to more toxic compounds.

Bioaccumulation, or bioconcentration, is a complex, dynamic process that depends on the availability, persistence, and physical and/or chemical properties of a compound in the environment. In general, pharmaceuticals tend not to be very lipophilic and are produced and/or used in relatively low quantities compared to industrial chemicals. In humans, the majority of pharmaceuticals are metabolized to some extent to SRSs that are more polar, less toxic, and less pharmacologically active than the parent compound. This suggests that there is a low potential for bioaccumulation or bioconcentration of pharmaceuticals; however, because of the length of time it takes to conduct chronic toxicity studies, applicants are encouraged to identify as early as possible compounds that are candidates for these studies.

A primary indicator of the potential for bioaccumulation is a compound's octanol/water partition coefficient (K_{ow}). A high octanol/water partition coefficient indicates that the compound will tend to be lipophilic. Chronic toxicity testing should be considered if log K_{ow} of a compound is greater

than or equal to 3.5 under relevant environmental conditions (e.g., pH 7), and a justification should be provided if chronic toxicity testing is not performed. Structural features (e.g., molecular size, polarity) that limit passage across biological membranes or the lack of bioavailability to environmental organisms (e.g., strong adsorption to soil) are mitigating factors that could be considered when determining if bioaccumulation (bioconcentration) would be a concern for compounds with a K_{ow} greater than or equal to 3.5. It may be important to obtain acute toxicity data for the organism to be tested to set the concentrations for the chronic studies properly. If the preparer of an EA is considering initiating chronic toxicity studies, consultation with CDER or CBER is recommended to ensure that such studies are appropriate and properly designed.

For chronic toxicity testing, if the EC_{50} or LC_{50} divided by the MEEC is greater than or equal to 10, no further testing should be conducted unless sublethal effects are observed at the MEEC. CDER or CBER should be consulted if the EC_{50} or LC_{50} divided by the MEEC is less than 10 or there are sublethal effects at the MEEC.

Test Methods and Test Organisms: Studies should be performed using test organisms and methods that have been identified by the FDA *Environmental Assessment Technical Handbook*, the EPA (40 CFR 797), the Organization for Economic Cooperation and Development (OECD), or other peer-reviewed literature, as appropriate, for use in environmental studies. If the drug or biologic product is intended to act upon an environmental organism (e.g., antiparasitic, antibiotic), information regarding the toxicity to the target organism(s) should be included.

c. Summary

A summary discussion of the environmental fate and effect of the substance(s) of interest should be provided. Discussion of the affected environments (aquatic, terrestrial, or atmospheric) should be included. The toxicity test results should be compared to the MEEC and the difference between the values discussed (e.g., in terms of the assessment factor, > 1000, > 100). It also may be appropriate to relate the toxicity test results to other estimated environmental concentrations (see section IV.B.1.a.iv).

2. Use of Fauna or Flora

If an EA is to be submitted for an action because the use of fauna or flora is the environmental issue (see section III.C.2 or 3), the EA should include specific information regarding the source of the fauna or flora, the mitigation measures associated with the harvesting of the resources, and a discussion of the reasonable

alternatives.

a. Use of Resources

Information relating to the source of the plant or animal, such as biological identification, government oversight of harvesting, geographic region where biomass is obtained, and harvesting methods and techniques should be included in the EA. The EA should include, but not be limited to, the following types of information:

- Biological identification (i.e., common names, synonyms, variety, species, genus, and family).
- A statement as to whether wild or cultivated specimens are used.
- The geographic region (e.g., country, state, province) where biomass is obtained and whether harvesting occurred on public or private land.
- A brief description of government oversight of the harvesting including, if applicable, the identity of the authority permitting harvesting and identity of authorities consulted regarding the harvesting. Submission of copies of permits or harvesting regulations relating to the specific species is helpful. For species covered under CITES, CDER or CBER could request copies of relevant permits.
- A brief description of the applicant's oversight of the harvesting.
- A statement indicating whether the species is (1) determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened, (2) entitled to special protection under some other Federal law or international treaty to which the United States is a party, or (3) the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or is entitled to special protection under some other Federal law or international treaty to which the United States is a party.
- A statement describing the part of plant or animal used and whether it is a renewable resource.

- A detailed description of the method of harvest including such information as the type of harvesting (e.g., clear cut, gleaning from timber stands destined for clear cutting, salvaging, pruning), frequency of harvest, whether the harvesting technique will affect the ecosystem (and if so, how), and whether the harvesting is conducted in accordance with government regulations or guidances (include citations to applicable regulations or guidances).

- Bulk weight or other appropriate measure of biomass needed to yield one kilogram of active moiety or biologic substance, the amount that has been harvested to date to support the proposed Agency action for the product, and the amount expected to be harvested in the future.

- The amount of biomass needed to produce the active moiety or biological substance used to treat the average patient. This should be provided in terms easy to understand (e.g., 2-3 trees per patient). The expected patient population and number of kilograms of active moiety or biologic substance needed per year should be provided.

- An estimate of the total number of plants or animals in the geographic region where the biomass is obtained.

- Any uses of the plant or animal other then for the proposed use (humans, food source, habitat for fauna).

- Plant or animal growth rate and/or life span and, if applicable, the rate of reproduction/regeneration.

- A discussion of whether the harvesting provides for sustained yield (e.g., percentage of sustainable harvest needed to supply annual needs based on the proposed use and any prior approved uses).

b. Mitigation Measures

Mitigation measures taken before (e.g., developing a process that uses a renewable part of a plant), during (e.g., limiting/selecting specimens to be harvested), and after harvesting (e.g., reforestation) should be included in the discussion of mitigation measures (see 40 CFR 1508.20).

c. Alternatives to the Proposed Action

A discussion must be provided of the reasonable alternatives that were considered when deciding which biomass source would be used to produce the active moiety or biologic substance (21 CFR 25.40(a)). All alternatives that were considered (e.g., other species, wild or cultivated sources, chemical synthesis) should be discussed. A brief discussion of the factors (e.g., environmental effects) that were considered in deciding whether or not the alternative would be used should be provided. The no-action (i.e., no approval) alternative should also be discussed. It should be indicated if any of the alternatives not currently used are planned for use in the future.

C. Data Summary Table

To facilitate review, the EA, if appropriate, should include a data summary table in a nonconfidential appendix (EA format item 11). Attachment E provides an example of a suitable data summary table.

D. Test Methods and Report Formats

Test methods and report formats are provided in the FDA *Environmental Assessment Technical Handbook*. Equivalent tests, such as those provided by the EPA (40 CFR 796 and 797), the Organization for Economic Cooperation and Development (OECD), or other validated, peer-reviewed methods can be used. Environmental fate studies should be compliant with either FDA's current Good Manufacturing Practice (cGMP) regulations (21 CFR 211.194) or FDA's Good Laboratory Practice (GLP) regulations (21 CFR part 58). The reports submitted in support of fate testing should include a description of the test method sufficient for a reviewer to determine the scientific merit of the methodology. Test performance and test reporting for environmental effects studies should meet FDA's GLP standards. Guidance on test reporting formats is included in the FDA *Environmental Assessment Technical Handbook* or 40 CFR parts 796 and 797. Raw test data (e.g., copies of notebook pages, HPLC chromatograms for each assay) should not be included in the EA.

E. Confidential and Nonconfidential Information

Some of the information that is submitted in an EA may be available elsewhere in an application or in a publicly available document. This information may be incorporated by reference in the EA (21 CFR 25.40(d)). However, the EA summary document, the document that contains the information recommended in section IV.A, should be a stand-alone document that contains a summary of the public information that is incorporated by reference and, to the extent possible, a summary of the confidential information that is either incorporated by reference or included in confidential appendices to the EA (21 CFR 25.51(a)). The EA will be made public by the FDA as required by regulations issued by

the Council on Environmental Quality. Therefore, the EA should contain, if appropriate, three distinct parts: (1) the EA summary document (see section IV.A), which is nonconfidential; (2) nonconfidential appendices; and (3) appendices with confidential information used to support the EA. Confidential data and information pertinent to the environmental review of a proposed action should be included in confidential appendices whenever possible to facilitate review of the EA. All confidential appendices should be at the end of the environmental assessment document. References to nonconfidential and confidential appendices may be included in the EA summary document, as appropriate. The EA summary document, nonconfidential appendices, and FONSI are made available for public inspection to the extent allowed by applicable laws (21 CFR 25.50(a) and (b)).

Attachment F provides general guidance as to which information can be included in confidential appendices of the EA. It is the applicant's responsibility to clearly identify the information in the EA that it believes is confidential.

F. Master Files for Drugs and Biologics

CDER and CBER do not take action on drug master files (DMFs) or master files (MFs) (i.e., they do not approve or disapprove submissions to a DMF (21 CFR 314.420(a)) or MF). Therefore, NEPA does not apply, and no EA needs to be submitted for a master file.

However, if an EA is required for the particular application, certain information that is included in a master file may be needed to address the relevant environmental issue(s). In these instances, the applicant seeking marketing approval should include the nonconfidential information in the EA summary document, rather than provide reference to the master file. The master file holder may be the applicant or an independent manufacturer who wants to limit the applicant's access to proprietary information. A master file reference may be provided for the confidential information, although this information must be summarized to the extent possible and included in the EA for public release. To expedite review of the EA, CDER and CBER prefer that copies of confidential information from master files be submitted in confidential appendices to the EA, whenever possible. If a letter of authorization is provided to reference confidential information in a master file, the specific type of information that is being referenced, the submission date, and page number where the information can be located should be stated. References to master files should be included in a confidential appendix since such references are considered confidential commercial information under the Freedom of Information Act (FOIA).

REFERENCES

1. FDA, "National Environmental Policy Act; Revision of Policies and Procedures; Final Rule," *Federal Register*, July 29, 1997 (62 FR 40569).

2. FDA, "National Environmental Policy Act; Proposed Revision of Policies and Procedures; Proposed Rule," *Federal Register*, April 3, 1996 (61 FR 14922); (republished May 1, 1996 (61 FR 19476)).

3. Rand, G., and S. Petrocelli, *Fundamentals of Aquatic Toxicology*, Hemisphere Publishing Corporation, 1987.

4. Zeeman, M., and J. Gilford, "Ecological Hazard Evaluation and Risk Assessment Under EPA's Toxic Substances Control Act (TSCA): An Introduction," *Environmental Toxicology and Risk Assessment, ASTM STP 1179*, Wayne G. Landis, Jane S. Hughes, and Michael A. Lewis, Eds., American Society for Testing and Materials, Philadelphia: 1993, pp. 7-21.

ATTACHMENT A: NO INCREASED USE

The following are types of actions that are not considered to result in increased use of an active moiety if approved by the Agency:

- Chemistry, manufacturing and control supplements (§§ 314.70, 601.12).
- Abbreviated applications.
- Lower doses than previously approved for the same indication (i.e., total daily dose).
- Shorter duration of use than previously approved for the same indication (e.g., number of days).
- Exclusion of a patient population in the labeling (e.g., by age, sex, complicating medical conditions).
- A prodrug for which the active metabolite is an approved product in the United States and which is intended to substitute directly[4] for that approved product. An active moiety which is the active metabolite of an approved prodrug in the United States would be considered similarly.
- New dosage forms that substitute directly for an approved product.
- Product reformulations in which the labeled amount of active moiety/biologic substance remains constant.
- Packaging changes/dosage form product line extensions that substitute directly for an approved product (e.g., new delivery system, addition of a different vial fill size).
- Combination drugs in which the single product substitutes directly for two approved products that would be administered separately.

[4] In context of Attachments A and B, substitute directly means that the drug or biologic product (i.e., active moiety or biologic substance) will be used for the same indication, at the same or lower dosage levels (i.e., total daily dose), and for the same or shorter duration of use (e.g., number of days) as previously approved by the Agency for the same active moiety or biologic substance.

ATTACHMENT B: INCREASED USE

The following are types of actions that are considered to result in increased use of an active moiety if approved by the Agency:

- New molecular entities.
- A new indication for a drug that was previously approved. This includes those actions requesting approval of off-label uses and switches from a second-line to first-line indication.
- R to OTC switches.
- Higher doses than were previously approved (i.e., total daily dose).
- Longer duration of use than previously approved (e.g., number of days).
- Inclusion of a patient population in the labeling that had previously been ***specifically excluded*** (e.g., by age, sex, complicating medical conditions).
- New dosage forms/routes of administration that increase the amount of active ingredient/biologic substance used. For example, the use of the active moiety or biologic substance for the same indication will normally increase if a switch is made from an injectable dosage form to an oral dosage form.

ATTACHMENT C: 40 CFR 1508.27

§ 1508.27 Significantly.

"Significantly" as used in NEPA requires considerations of both context and intensity:

(a) *Context.* This means that the significance of an action must be analyzed in several contexts such as society as a whole (human, national), the affected region, the affected interests, and the locality. Significance varies with the setting of the proposed action. For instance, in the case of a site-specific action, significance would usually depend upon the effects in the locale rather than in the world as a whole. Both short- and long-term effects are relevant.

(b) *Intensity.* This refers to the severity of impact. Responsible officials must bear in mind that more than one agency may make decisions about partial aspects of a major action. The following should be considered in evaluating intensity:

(1) Impacts that may be both beneficial and adverse. A significant effect may exist even if the Federal agency believes that on balance the effect will be beneficial.

(2) The degree to which the proposed action affects public health or safety.

(3) Unique characteristics of the geographic area such as proximity to historic or cultural resources, park lands, prime farmlands, wetlands, wild and scenic rivers, or ecologically critical areas.

(4) The degree to which the effects on the quality of the human environment are likely to be highly controversial.

(5) The degree to which the possible effects on the quality of the human environment are highly uncertain or involve unique or unknown risks.

(6) The degree to which the action may establish a precedent for future actions with significant effects or represents a decision in principle about a future consideration.

(7) Whether the action is related to other actions with individually insignificant but cumulatively significant impacts. Significance exists if it is reasonable to anticipate a cumulatively significant impact on the environment. Significance cannot be avoided by terming an action temporary or by breaking it down into small component parts.

(8) The degree to which the action may adversely affect districts, sites, highways, structures, or objects listed in or eligible for listing in the National Register of Historic Places or may cause loss or destruction of significant scientific, cultural, or historical resources.

(9) The degree to which the action may adversely affect an endangered or threatened species or its habitat that has been determined to be critical under the Endangered Species Act of 1973.

(10) Whether the action threatens a violation of Federal, State, or local law or requirements imposed for the protection of the environment.

ATTACHMENT D: EA FORMAT

1. **Date**
2. **Name of Applicant/Petitioner**
3. **Address**
4. **Description of Proposed Action**
    a. **Requested Approval**
    b. **Need for Action**
    c. **Locations of Use**
    d. **Disposal Sites**
5. **Identification of Substances that are the Subject of the Proposed Action**
    a. **Nomenclature**
        i. **Established Name (U.S. Adopted Name - USAN)**
        ii. **Brand/Proprietary Name/Tradename**
        iii. **Chemical Names or Genus/Species of Biologic Product (e.g., virus)**
            - **Chemical Abstracts (CA) Index Name**
            - **Systematic Chemical Name**
    b. **Chemical Abstracts Service (CAS) Registration Number**
    c. **Molecular Formula**
    d. **Molecular Weight**
    e. **Structural (graphic) Formula/Amino Acid Sequence**
6. **Environmental Issues**
7. **Mitigation Measures**
8. **Alternatives to the Proposed Action**
9. **List of Preparers**
10. **References**
11. **Appendices**

ATTACHMENT E: SAMPLE DATA SUMMARY TABLE

SAMPLE DATA SUMMARY TABLE	
PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility[1]	
Dissociation Constant(s)	
Log Octanol/Water Partition Coefficient (Log K_{ow})[1]	
Vapor Pressure or Henry's Law Constant	
Sorption/Desorption (K_{oc})[1]	
DEPLETION MECHANISMS	
Hydrolysis	
Aerobic Biodegradation	
Soil Biodegradation	
Photolysis	
Metabolism	
ENVIRONMENTAL EFFECTS[2]	
Microbial Inhibition	
Acute Toxicity	
Chronic Toxicity	

[1]Depending on dissociations constant(s), water solubility and octanol/water partition coefficient may have to be determined at pH 5 and 9, in addition to pH 7 or K_{oc} may have to be determined in acidic and/or alkaline soil in addition to neutral soil. See section IV.B.1.a.ii for guidance.

[2]Identify organism(s) and report results, e.g., NOEC, MIC, EC_{50}, LC_{50} in ppm of active moiety.

ATTACHMENT F: CONFIDENTIAL/NONCONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NONCONFIDENTIAL	CONFIDENTIAL
1.Date	***	X	
2. Name of Applicant/Petitioner	***	X	
3. Address	***	X	
4. Description of Proposed Action	a. Requested Approval	X	
	b. Need for Action	X	
	c. Locations of Use	X	
	d. Disposal Sites	X	
5. Identification of Substances that are the Subject of the Proposed Action	a. Nomenclature	X	
	b. CAS Number	X	
	c. Molecular Formula	X	
	d. Molecular Weight	X	
	e. Structural Formula	X	

EA FORMAT ITEM	SUBSECTION	NONCONFIDENTIAL	CONFIDENTIAL
6. Environmental Issue (Specific environmental issues identified in section IV.B)	a. Assessing Toxicity to Environmental Organisms	For example: * Substances expected to enter or exist in the environment. * Summary discussion of toxicity/activity of predominant SRSs relative to the parent (active) compound * Test results physical/chemical characterization * Method of calculating estimates of environmental concentration * Supporting information for spatial/temporal depletion factors * Environmental effects test results	For example: * Specific toxicology/ pharmacological activity data for SRSs * Test reports * Environmental concentration estimates
	b. Use of Fauna or Flora	For example: * Biological identification and other information relating to species used (e.g., plant growth rate) * Geographic region of the source * Government oversight * Method of harvesting	For example: * Bulk weight of biomass needed to produce a kg of active moiety * Amount harvested * The expected patient population and kg of active moiety expected to be used per year
7. Mitigation Measures	***	X	
8. Alternatives to the Proposed Action	***	X	
9. List of Preparers	***	X	

EA FORMAT ITEM	SUBSECTION	NONCONFIDENTIAL	CONFIDENTIAL
10. References	***	X	
11. Appendices	***	For example: * Referenced articles not generally available or which are used to support specific claims in the EA document * Data summary table	For example: * Estimates of the kg of active moiety to be used/year * Test reports * Letters of authorization to DMFs

ATTACHMENT G: GLOSSARY OF TERMS

Active Moiety: The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance (21 CFR 314.108(a)). The active moiety is the entire molecule or ion, not the "active site."

Bioaccumulation: The process by which industrial waste, chemicals, and other substances gradually accumulate in living tissue.

Bioconcentration: The process by which industrial waste, chemicals, and other substances accumulate directly from water into and onto aquatic organisms.

Biological (biologic) product: Any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component, derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings (section 351 of the Public Health Service Act).

Biomass: The plant, plant part (e.g., bark, leaves, flower, seed), animal, or animal part (e.g., skin, liver, stomach) that is collected for processing into a drug or biologic.

Drug product: A finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more ingredients (21 CFR 314.3(b)).

Drug substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

Expected environmental concentration (EEC): The expected concentration of the active moiety or other structurally related substance of interest that organisms would be exposed to in the environment (e.g., surface water) after consideration of spatial or temporal concentration or depletion factors such as dilution, degradation, sorption, bioaccumulation. This is sometimes referred to as the predicted environmental concentration (PEC).

Expected introduction concentration (EIC) for disposal: The expected introduction concentration of the active moiety that may enter the environment due to disposal. Depletion mechanisms that occur prior to introduction into the environment may be considered in the calculation as indicated in the text.

Expected introduction concentration (EIC) for use: The expected introduction concentration, based on fifth-year marketing estimates, of the active moiety that can enter the environment due to use. Depletion mechanisms that occur prior to introduction into the environment and human metabolism may be considered in the calculation as indicated in the text.

Half-life ($t_{½}$): Time required to reduce by one-half the concentration of a material.

Lowest observed effect concentration (LOEC): The lowest concentration of a material used in a toxicity test that has a statistically significant adverse effect on the exposed population of the test organisms as compared with the controls.

Master file: A submission of information to the FDA by a person who intends it to be referenced during the review of an application. See 21 CFR 314.420 for specific information on drug master files.

Maximum expected environmental concentration (MEEC): The expected introduction concentration (EIC) or expected environmental concentration (EEC), whichever is greater.

Median effective concentration (EC_{50}): The concentration of material to which organisms are exposed that is estimated to be effective in producing some sublethal response in 50 percent of the test organisms. The EC_{50} is usually expressed as a time-dependent variable (e.g., 24 hour EC_{50}).

Median lethal concentration (LC_{50}): The concentration of material to which organisms are exposed that is estimated to be lethal to 50 percent of the test organisms. The LC_{50} is usually expressed as a time-dependent variable (e.g., 24 hour LC_{50}).

Minimum inhibitory concentration (MIC): The lowest concentration of a chemical that inhibits the visible growth of the test organisms.

New molecular entity: An active moiety (present as the unmodified base [parent] compound, or an ester or a salt, clathrate, or other noncovalent derivative of the base [parent] compound) that has not been previously approved or marketed as the active moiety in the United States for use in a drug product, either as a single ingredient or as part of a combination product, or as part of a mixture of stereoisomers.

No observed effect concentration (NOEC): The highest concentration of a material used in a toxicity test that has no statistically significant adverse effect on the exposed population of test organisms as compared with the controls.

Octanol/water partition coefficient (K_{ow}): The ratio of a chemical's solubility in n-octanol and water at equilibrium; also expressed as P. A measurement of a drug's or biologic's lipophilicity and an indication of its ability to cross cell membranes. The logarithm of P or K_{ow} is used as an estimate of the tendency of the chemical to bioaccumulate or adsorb to soil or sediments.

Parts per billion (ppb): One unit of chemical (usually expressed as mass) 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 = 1 ppb; for tissue 1 µg/kg = 1 ng/g = 1 ppb.

Parts per million (ppm): One unit of chemical (usually expressed as mass) per 1,000,000 (10^6) units of medium (e.g., water) or organism (e.g., tissue) in which it is contained. For water 1 mg/L = 1 ppm; for tissue 1 mg/kg = 1 µg/g = 1 ppm.

Parts per trillion (pptr): One unit of chemical (usually expressed as mass) per 1,000,000,000,000 (10^{12}) units of medium (e.g., water) or organism (e.g., tissue) in which it is contained. For water 1 ng/L = 1 pptr; for tissue 1 ng/kg = 1 pptr.

Soil or sediment/water partition coefficient (K_{oc}): The ratio of chemical adsorbed per unit weight of organic carbon in soil or sediment to the concentration of the chemical in solution at equilibrium.

Toxicity: The inherent potential or capacity of a material to cause adverse effects in a living organism.