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Environmental assessment: U.S. requirements in new drug applications*

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Abstract

The Food and Drug Administration (FDA), under the Federal Food, Drug and Cosmetic (FD&C) Act and other public health statutes, is responsible for ensuring that human drugs are safe and effective. FDA is able to carry out its responsibilities by approving products before they are marketed, enforcing regulations, and taking necessary compliance actions when problems are identified. The National Environmental Policy Act (NEPA) provides FDA with supplementary authority to consider environmental factors in its decisionmaking. The role of the FDA Center for Drug Evaluation and Research in implementing NEPA is discussed.

1. Introduction

The Food and Drug Administration (FDA), under the Federal Food, Drug and Cosmetic (FD&C) Act and other public health statutes, is responsible for ensuring that (1) food is safe and wholesome; (2) human and animal drugs, biological products, and medical devices are safe and effective; (3) cosmetics are safe; (4) radiological products do not result in unnecessary radiation exposure; and (5) products are honestly and informatively labeled. FDA is able to carry out its responsibilities by (1) approving products before they are marketed, (2) promulgating regulations, and (3) taking necessary compliance actions when problems are identified.

The National Environmental Policy Act (NEPA) provides FDA with supplementary authority to consider environmental factors in decisionmaking. NEPA establishes a broad mandate for Federal agencies to protect and enhance all aspects of the human environment. The Act declares national

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environmental policy and states goals and a method for accomplishing the policy and goals through action-forcing provisions. The heart of the action-forcing provisions, is in § 102(2) (C), which requires that, before taking an action, Federal agencies must prepare a detailed Environmental Impact Statement (EIS) for every major action significantly affecting the quality of the human environment. The role of the FDA Center for Drug Evaluation and Research in implementing NEPA is the subject of the present paper.

2. The FDA organization

The FDA is administratively divided into action units of which the four separate Centers for (1) Drugs, (2) Biologics, (3) Foods, and (4) Veterinary Medicine are the principle components for implementing NEPA actions. Within the Center for Drug Evaluation and Research (CDER), the principle environmental actions are categorical exclusions, environmental assessments with Findings of No Significant Impact (FONSI's), and Environmental Impact Statements (EIS's). The most frequent actions are categorical exclusions which are certain FDA actions which *ordinarily* do not require the preparation of an EA (Environmental Assessment) because, as a class, these actions will not result in the production or distribution of any substance and, therefore, will not result in the introduction of any substance into the environment.

2.1 Environmental assessments

Indeed, 97% of FDA actions are categorically excluded from the requirement for an environmental assessment. The environmental assessments constitute 3% with two-thirds requiring a "full" environmental assessment and one-third requiring an abbreviated environmental assessment. Of the roughly 13,000 categorical exclusions, the CDER accounts for 50% of the actions.

Looking at the number of abbreviated environmental assessments, we see that CDER has about 18% of the actions. The full environmental assessments constitute 70% of CDER actions. It should be noted that in CDER at any one time there are roughly 200 New Drug Applications in the pipeline requiring environmental assessments and about 6,000 Investigational New Drug applications requiring either an environmental assessment or a categorical exclusion.

3. Implementation of NEPA by CDER

How is CDER implementing NEPA? To comply with the policies and goals of NEPA, the President's Council on Environmental Quality (CEQ) regulations, and FDA's policies and procedures, certain requirements must be met. These requirements are specified as follows:

1. Adopt necessary procedures to supplement the CEQ regulations (§ 1507.3(a)).

FDA's final NEPA-implementing procedures (21 CFR Part 25) were published in the Federal Register in 1985.

2. Specify in Agency procedures the criteria for and identification of those typical classes of actions that (1) normally require an EIS, (2) are categorically excluded, (3) normally require an environmental assessment (EA), but not necessarily an EIS (§ 1507.3(b)(2)).

There are no categories of FDA actions that routinely require the preparation of an EIS. An EIS is prepared if an evaluation of the data in an EA shows that a proposed action may significantly affect the quality of the human environment (21 CFR 25.21). Therefore, FDA actions ordinarily require an EA, unless they qualify for a categorical exclusion. (as specified in §§ 25.23 and 25.24).

An action that qualifies for categorical exclusion does not require either an EA or an EIS because the action (1) will not result in introduction of any substance into the environment, (2) meets specific criteria that are intended to ensure that it will cause no significant environmental effects, or (3) is a routine maintenance or minor leasing or construction activities conducted for or contacted for by FDA. Section 25.34 lists the excluded actions along with any applicable criteria for the exclusion.

3. Prepare the required environmental documents, i.e., Finding Of No Significant Impact (FONSI), EA, draft, final, and supplemental EIS (§§ 1501.3, 1501.4, and 1502).

FDA's procedures and formats for preparing and submitting environmental documents are provided for in Part 25. (§§ 25.30, 25.31, 25.32, 25.33, 25.34, 25.40, and 25.42.) Most FDA actions, including those initiated by industry sponsors, do not require a detailed EA; they belong to one or more classes of actions that are categorically excluded from environmental review under appropriate regulatory provisions (§ 25.24) or qualify for an abbreviated EA (§ 25.31a(b)).

4. Provide for public involvement in the environmental review and decisionmaking process (§ 1506.6).

Procedures for involving the public are specified in §§ 25.41(b) and 25.42(b). The FDA Center for Drug Evaluation and Research is developing and implementing procedures for making EA's and FONSI's available to the public, e.g., by periodically (2–4 times per year) publishing a list of available EA's and FONSI's in the Federal Register. If, after publishing the list of EA's and FONSI's, new information becomes available to FDA suggesting that a human drug approval may significantly affect the environment, the Agency may consider the need for an EIS under the retroactive provision (§ 25.25).

5. Adopt procedures for incorporating environmental considerations as an integral part of the decisionmaking process (§ 1505.1).

FDA's procedures for incorporating environmental factors in decisionmaking are specified (§ 25.40 and § 25.42(b)(5)(i)). The policy and procedures guides for processing NDA's etc., incorporate consideration of environmental impact as an integral part of the NDA, etc., process in order to ensure that the

environmental considerations are initiated early in the review process and concurrently with other considerations.

6. Assist applicants required to submit environmental information by outlining the types of information required (§ *1506.5*(*a*)).

The information required to be submitted by an industry sponsor to claim a categorical exclusion is specified in the regulations (§ 25.23).

Section 25.31a provides formats for EA's for environmental actions. FDA has prepared an assistance document entitled Environmental Assessment Technical Assistance Handbook (FDA/CFSAN-87/30) which describes approaches for the efficient preparation of environmental assessments, protocols for environmental tests, and the interpretation of results of such tests.

7. Ensure the completeness and accuracy of information provided by applicants in EA's and in claims for categorical exclusion (§ *1506.5*(*a*) *and* (*b*)).

FDA procedures for meeting this requirement are specified (§§ 25.22(d), and 25.32(c) and 25.41(c)). For actions requiring a FONSI, the Center must ensure that information in an applicant's EA is complete and accurate, and the Agency must prepare the FONSI. The Agency official responsible for preparing and approving the FONSI must sign the document to show that they approve the conclusions not to prepare an EIS. The most appropriate way to determine the accuracy of the testing data is to have the studies made under the procedures of Good Laboratory Practice described at 21 CFR Part 58.

8. Provide in Agency procedures for extraordinary circumstances in which a normally excluded action may have a significant environmental impact (§ *1508.4*).

FDA meets this requirement (§ 25.23(b)).

9. Utilize a systematic, interdisciplinary approach which will ensure the integrated use of natural and social sciences in planning and decisionmaking (§ *1507.2*).

The FDA Center for Drug Evaluation and Research supplements existing resources by relying on other scientists in FDA and scientists in other Federal agencies, particularly EPA.

The above represents some of the activities pertinent to the NEPA review processes for NDA's and IND's. Specific perspectives on NEPA management follow:

The Center for Drug Evaluation and Research has always required NEPA actions as part of the drug approval process. The Center initiated full NEPA Compliance in January, 1990 for new molecular entities (NME's) in the environmental assessments in the NDA's. The NDA's for NME's constitute about 25–40 actions per year and are completely reviewed. Environmental considerations for IND's are generally made by the reviewing chemists. However, all environmental actions by the Center come under the responsibility of the Center's Environmental Assessment Officer (EAO). With respect to NDA's, FDA/CDER had initially reviewed only NME's fully. Under NEPA, however, all actions must have an environmental review. There is no "grandfathering" of actions.

Actions may be categorically excluded only if the exclusion meets the criteria set forth in Sections 25.23 and 25.24. For all NDA's, there must be data available to the Agency that does not establish that, at the expected levels of exposure, the substance may be toxic to organisms in the environment; and for IND's, if the drug shipped under such notice is intended to be used for clinical studies or research in which waste will be controlled or the amount of waste expected to enter the environment may reasonably be expected to be non-toxic.

These criteria also apply to the promulgation, revocation, or amendment of a monograph for a drug that is not a new drug, for an antibiotic drug, or for an over-the-counter (OTC) drug, if the drug is already marketed.

As FDA moves forward in its implementation of NEPA, and gains experience in evaluating environmental assessments, standards will become higher and more stringent. Applicants should no longer treat the environmental assessment as a stepchild of the NDA. FDA has already encountered instances where a finding of no significant impact cannot be determined but that an Environmental Impact Statement is required. Applicants need to pay close attention to mitigation measures in an attempt to avoid having the agency prepare an EIS.

4. Data verification management

The Handbook (FDA/CFSAN-87/30) states that the expected level of test performance and test reporting should meet the standards of FDA's Good Laboratory Practice (GLP) regulations. The CEQ regulations discuss in detail at 40 CFR 1506.5 the Agency's responsibility when environmental information is required from applicants:

(a) *Information.* If an agency requires an applicant to submit environmental information for possible use by the agency in preparing an environmental impact statement, then the agency should assist the applicant by outlining the types of information required. The agency shall independently evaluate the information submitted and shall be responsible for its accuracy. If the agency chooses to use the information submitted by the applicant in the environmental impact statement, either directly or by reference, then the names of the persons responsible for the independent evaluation shall be included in the list of preparers (1502.17). It is the intent of this paragraph that acceptable work not be redone, but that it be verified by the agency.

(b) *Environmental assessments.* If an agency permits an applicant to prepare an environmental assessment, the agency, besides fulfilling the requirements of paragraph (a) of this section, shall make its own evaluation of the environmental issues and take responsibility for the scope and content of the environmental assessment.

FDA's mechanism of requiring environmental information from applicants, FDA's obligation to provide guidance on how to acquire that information, and FDA's obligation to verify the information is paramount to environmental review. Inability of FDA to verify the methodology used to develop information

or to have access to the raw data from the study will not permit FDA to make a decision about whether to approve a product or whether mitigations are required. The Good Laboratory Practice regulations have been used to ensure data integrity for environmental studies as such studies are nearly 100% non-clinical. FDA inspects environmental studies, just like other non-clinical laboratory studies, and uses inspection reports in determining the validity of the studies.